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Pre-authorisation Evaluation of Medicines for Human Use

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WITHDRAWAL ASSESSMENT REPORT FOR

BOSATRIA

International Nonproprietary Name:

MEPOLIZUMAB

Procedure No.: EMEA/H/C/1069

Day 180 Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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LIST OF ABBREVIATIONS

AE adverse event
AILD angioimmunoblastic T-cell lymphoma with dysproteinemia
ANCOVA analysis of covariance
CL clearance
Cmax maximum plasma concentration
CNS central nervous system
CHMP Committee for Human Medicinal Products
CRF case report form
CRT collaborative research trial
Cs observed concentration
CSR clinical study report
CT computed tomography
CTD Common Technical Document
CV cardiovascular
DNA deoxyribonucleic acid
ECG electrocardiogram
ECP eosinophil cationic protein
EDN eosinophil derived neurotoxin
EE eosinophilic esophagitis
EGD esophagogastroduodenoscopy
EU European Union
EW early withdrawal
FDA Food and Drug Administration
FIP1 positive FIP1L1-PDGFRα fusion gene present
FIP1 negative FIP1L1-PDGFRα fusion gene absent
GI gastrointestinal
GM-CSF granulocyte-macrophage colony-stimulating factor
GSK GlaxoSmithKline
hERG human ether-a-go-go related gene
HES hypereosinophilic syndrome
hIL-5 human interleukin-5
IC50 concentration which inhibits 50% of activity
IL-3 interleukin-3
IL-5 interleukin-5
IM intramuscular
Imax maximum inhibition
ITT Intent-to-Treat
IV intravenous
LFTs liver function tests
LOCF last observation carried forward
mAb monoclonal antibody
MBP major basic protein
MedDRA Medical Dictionary for Regulatory Activities
mg milligram
NA North America
NHL non-Hodgkin's lymphoma
NPS Named Patient Supply
PC20 20% fall in forced expiratory volume in one second (FEV1)
PD pharmacodynamics

PFTs pulmonary function tests
PIL Patient Information Leaflet

PIP Pediatric Investigation Plan
PK pharmacokinetics
pVAS Pruritus Visual Analog Scale
RBC red blood cell(s)
ROW Rest of World
SAWP Scientific Advice Working Party
SAE serious adverse event
SC subcutaneous
SD standard deviation
SEER Surveillance, Epidemiology and End Results
SmPC/SPC Summary of Product Characteristics
SOC system organ class
T1/2 half-life
tmax time-to-maximum concentration
TNF tumor necrosis factor
µL microliter
URTI upper respiratory tract infection
US United States
Vc volume of distribution of the central compartment
Vss volume of distribution at steady state

RECOMMENDATION

Based on the review of the data and the applicant's response to the CHMP LoQ on quality, safety and efficacy, the CHMP considers that the application for BOSATRIA (mepolizumab), an orphan medicinal product, in the treatment of adult patients with hypereosinophilic syndrome (HES) without the FIP1L1-PDGRF fusion gene, to reduce or eliminate the need for corticosteroid therapy and to reduce eosinophil count,

is not approvable since major objections still remain, which preclude a recommendation for marketing authorisation at the present time.

Inspection issues
GCP inspection is suggested in some centres, since no significant efficacy was reached in RoW population.

The drug substance manufacturing facilities should be inspected by an EU inspectorate and found to be in compliance with EU GMP.

I. EXECUTIVE SUMMARY

I.1 Problem statement

Hypereosinophilic syndrome (HES) is a myeloproliferative disorder characterized by persistent eosinophilia that is associated with damage to multiple organs. In 1975, Chusid et al defined the 3 features required for a diagnosis of hypereosinophilic syndrome:

1. A sustained absolute eosinophil count (AEC) greater than >1500/µl is present, which persists for longer than 6 months.
2. No identifiable aetiology for eosinophilia is present.
3. Patients must have signs and symptoms of organ involvement.

In HES, prolonged elevated eosinophil levels are known to be associated with end organ damage and/or dysfunction at various sites, most often heart, skin, lungs, nervous system, liver, and digestive tract [Wilkins, 2005]. Data from three patient series were combined and it was reported that 100% of HES patients exhibited eosinophilia, 58% had cardiovascular manifestations, 56% cutaneous, 54% neurologic, 49% pulmonary, 43% splenic, 30% hepatic, 23% ocular, and 23% gastrointestinal (GI) involvement [Sheikh, 2007]. Renal involvement of HES has also been described in the literature [Fauci, 1982; Richardson, 1994; Liapis, 2005]. The level or duration of blood eosinophilia does not necessarily correlate with the degree of end-organ damage in HES, although the severity of the clinical pathology does appear to reflect the extent of eosinophil activation in the tissues [Weller, 1994; Roufosse, 2006]. The cytokine IL-5 has been identified as the major haematopoietic responsible for the growth and differentiation [Clutterbuck, 1989], recruitment, [Wang, 1989] activation, and survival [Lopez, 1988] of eosinophils.

HES is managed initially with moderate-to-high dose corticosteroids to rapidly reduce blood eosinophils [Assa'ad, 2000; Katz, 2005; Klion, 2006]. Although not formally approved for HES, corticosteroid therapy has been used for decades in clinical practice and represents first line treatment for FIP1 negative HES both in the EU and elsewhere [Klion, 2006; Ogbogu, 2007]. Published guidance for the treatment of HES [Klion, 2006; Wilkins, 2005] suggests initial corticosteroid dosing regimens of 40-60 mg daily (or 1 mg/kg). Although many patients respond to treatment with corticosteroids, toxicity with long-term use and/or lack of efficacy lead to a variety of cytotoxic and immunomodulatory agents including hydoxyurea, vincristine, methotrexate, interferon alpha, immunoglobulin, and cyclosporine being used as second line agents. Many of these cause broad immunosuppression and are therefore associated with a range of serious toxicities and may confer an increased risk of developing malignancy. None of these therapies are approved for HES [Weller, 1994; Klion, 2006]. The impact of cumulative steroid toxicity is greater in

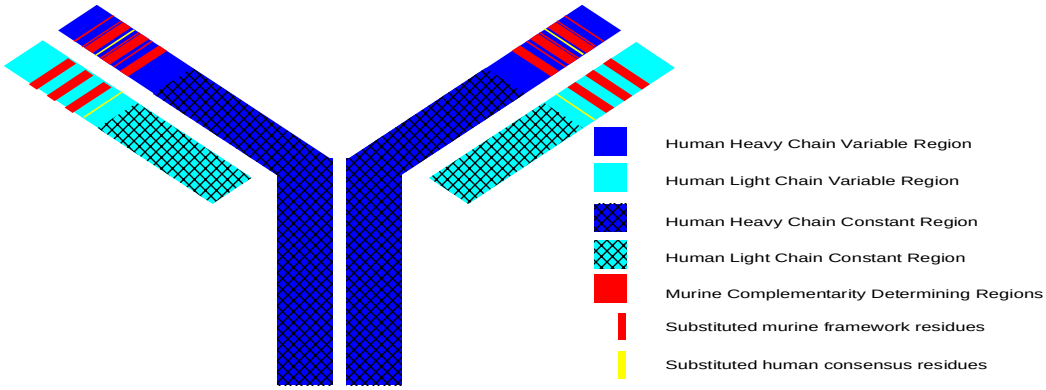
FIP1 negative patients as a result of greater corticosteroid responsiveness and use compared with FIP1 positive patients.

Glivec (imatinib mesylate) was approved in 2006 in the EU for the treatment of HES in patients who have the FIP1 mutation. However, it is not licensed for FIP1 negative patients in the EU. Use of imatinib may be complicated by the development of cardiac toxicity, GI intolerance, rash, and other side effects.

I.2 About the product

Mepolizumab is a fully humanised monoclonal IgG (IgG_1 kappa) antibody which binds to human IL-5 with both high specificity (IC_{50} <1 nM) and affinity (Kd = 4.2 pM), preventing it from binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface and thus inhibiting IL-5 signalling. IL-5 has been identified as the major cytokine responsible for the growth and differentiation recruitment, activation, and survival of eosinophils. The inhibition of IL-5 signalling caused by mepolizumab leads to decreases in the accumulation and activation of circulating eosinophils in the blood. The mepolizumab functional protein consists of two light and two heavy chains with a single disulphide bond covalently linking the heavy and light chains. The heavy chains of mepolizumab are also covalently linked to each other by disulphide bonds. Both the heavy chains are N-linked glycosylated and the oligosaccharides are estimated to be of complex biantennary nature. The molecular weight is 149.2 kDa including 3kDa of carbohydrate residues.

A schematic representation of the mepolizumab antibody structure:



The proposed indication is for the treatment of adult patients with hypereosinophilic syndrome without the FIP1L1-PDGFR fusion gene to:

- reduce or eliminate the need for corticosteroid therapy
- reduce blood eosinophil count.

The standard dose of mepolizumab is 750 mg administered by intravenous infusion, once every 4 weeks to achieve control and then at intervals of > 4 weeks thereafter, as appropriate.

Mepolizumab is an interleukin inhibitor for which the ATC code is L04AC06.

I.3 The development programme/Compliance with CHMP Guidance/Scientific Advice

The applicant has developed this product originally for the treatment of asthma and atopic dermatitis. As not enough efficacy was reached, the development for these indications has been stopped. Other indications other than HES in which mepolizumab have been given during the development includes eosinophilic oeasophagitis.

Following the initial asthma studies, mepolizumab was provided for compassionate use and investigator-led Collaborative Research Trials (CRTs) in patients with HES. Multiple factors contribute to asthma and atopic dermatitis and the role of the eosinophil in these indications is not as clearly defined. In contrast, eosinophilia is the key contributing factor in HES and plays a major role in the diagnosis, treatment and management of the disease. Based on preliminary clinical assessments, treatment with mepolizumab was well tolerated and resulted in clinically meaningful relief of signs and symptoms. As a result of the clinical benefit observed in HES, GSK consulted investigators and regulatory authorities to develop the design for a randomized, double-blind, placebo-controlled trial of 36 weeks duration to evaluate the effects of mepolizumab in allowing corticosteroid-sparing and blood eosinophil reduction in a disease-controlled population (Study MHE100185).

On 23 June 2003, the applicant GlaxoSmithKline requested scientific advice for their product mepolizumab pursuant to Article 51 (j) of Council Regulation No (EEC) 2309/93. Since HES is a rare, life-threatening disease with an unmet medical need, it was agreed with the Scientific Advice Working Party (SAWP) that one pivotal study may be sufficient for regulatory filing in support of this indication. The advice was not followed by the applicant on following aspects: 1) Bone marrow biopsies were not performed, but were removed from the protocol 2) End organ assessment was not performed very extensively. An additional advice was given in 2006 regarding the need for a full QT prolongation assessment; the CHMP recommended that the clinical follow-up in the phase III placebo-controlled trial should correspond to that proposed in the ICH E14 document. At a late stage, scientific advice was also given by national authorities (Germany, UK, Spain, France and Finland) on the mepolizumab clinical development programme and/or clinical trial results.

Study MHE100185 has now been completed. Following participation in Study MHE100185, eligible patients could enter a long-term, open-label extension study of mepolizumab, MHE100901, which is currently ongoing. In parallel to studies MHE100185 and MHE100901, there is an ongoing global compassionate use programme to treat patients with severe HES disease who have failed available therapies. The programme was initiated in 2001 and suspended in 2003 due to limitations in drug supplies. This programme was reinstated in 2005 and is implemented via a GSK-sponsored clinical trial in the US (MHE104317) and a Named Patient Supply (NPS) Program in Europe and Rest-of-World (ROW). Finally, mepolizumab is also being investigated in eosinophilic oesophagitis which is a rare inflammatory disease of the oesophagus, characterised by dense eosinophilic infiltration of unknown aetiology. An exploratory study in adults has been completed (MEE103226) and an exploratory study in paediatric patients is currently ongoing (MEE103219).

I.4 General comments on compliance with GMP, GLP, GCP

GMP: Manufacture, primary packaging, labeling, secondary packaging and release of the drug product is undertaken by GSK Parma, Italy. An inspection of the Parma facility is not anticipated as it is regularly inspected by AIFA. The next scheduled AIFA inspection of the Parma site was due in October 2008. Inspection of the drug substance manufacturing facilities should be considered as these sites have not been inspected by any EU Agency.

GLP: All of the definitive safety studies with mepolizumab and SB-264091 were performed in full compliance with Good Laboratory Practice (GLP) regulations. Other studies were performed in accordance with accepted scientific practice and in general agreement with the principles of GLP.

GCP: The applicant has stated that all studies were undertaken in accordance with standard operating procedures of the GlaxoSmithKline Group of Companies, which comply with the principles of Good Clinical Practice. All studies were conducted with the approval of Ethics Committees or Institutional Review Boards.

As for the single pivotal trial in HES (Study MHE100185), a single US investigator site was audited by the Worldwide Clinical Compliance Unit at GSK. Due to the rarity of the disease and the multiplicity of centres, the study would have benefited from closer monitoring and auditing as suggested by the number of protocol deviations detected and the number of early withdrawals to enter the open label extension study. A GCP inspection is suggested in all individual centers, since no significant efficacy was reached in RoW population.

I.5 Type of application and other comments on the submitted dossier

This application concerns a Centralised Procedure according to Regulation (EC) No 726/2004, Mandatory scope (Article 3(1)), Annex (1) (Biotech medicinal product) and Annex (4) (Orphan medicinal product). for Bosatria (mepolizumab, SB-240563). It is a full application under Article 8(3) of Directive 2001/83/EC for a new active substance. The product, BOSATRIA 250 mg lyophilised powder for infusion is intended for the treatment of adult patients with hypereosinophilic syndrome (HES) without the FIP1L1-PDGFR fusion gene to reduce or eliminate the need for corticosteroid therapy to reduce blood eosinophil count.

In general, the performed studies have been adequately performed and reported. No paediatric studies have been performed in the proposed indication. Some paediatric data have been gathered from compassionate use program. EMEA has made a decision on the application for agreement of a Paediatric Investigation Plan (PIP) for Mepolizumab (EMEA-000069-PIP01-07) on 20 July 2008. Overall, the dossier is of good quality. The pharmaceutical aspects of the dossier are, for the most part, very clear and concise although there are some contradictions within the submission that require clarification. The non-clinical data are presented in a very polished fashion, but a little more detail in the reports would have been better. The Pharmacology section of the Clinical Overview is not very well summarised. With regard to the Clinical section - as well as the study report of the pivotal HES trial – statistical analyses are discussed in details; however, there is a lack of clinical insight into the overall individual outcome of the patients (e.g., disease control), which is considered critical given the severity of the disease and the small size of the patient sample.

II. SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

BACKGROUND INFORMATION ON THE PRODUCT

Name of product	Bosatria
Applicant	Glaxo Group Ltd
Active substance	mepolizumab
INN	mepolizumab
Pharmaco-therapeutic group	L04AC06: immunosuppressant – interleukin inhibitor – mepolizumab

Therapeutic indication	Treatment of adult patients with hypereosinophilic syndrome without the FIP1L1-PDGFR fusion gene to reduce or eliminate the need for corticosteroid therapy and to reduce blood eosinophil count.
Substance group	Monoclonal antibodies
Source	IgG1κ monoclonal antibody produced from a CHO cell line

1. INTRODUCTION:

The drug substance mepolizumab is an anti-interleukin-5 (IL-5) recombinant humanised IgG1κ monoclonal antibody. Both heavy chains are glycosylated with complex biantennary oligosaccharides. The total molecular weight is approximately 149 kDa.

Mepolizumab is produced from CHO cells and a two-tiered cell banking system of Master Cell Bank (MCB) and Working Cell Bank (WCB) is used for the manufacture. The fermentation process is followed by a purification process that includes a series of chromatography steps, ultrafiltration step, viral inactivation and filtration steps.

The drug product manufacturing process consists of the sterile filtration of the formulated bulk drug substance, aseptic filling into vials, lyophilisation, stoppering and crimping of the vials.

Bosatria is presented as a concentrate (250 mg) for infusion to be reconstituted with water for injections and subsequently diluted with 0.9 % sodium chloride prior to administration.

2. DISCUSSION:

One Major Objection was identified at Day 120. The quality of the isoelectric focusing (IEF) gels provided, in addition to the broad acceptance limits adopted, suggested that the sensitivity of the current IEF method to detect all charged variants was not appropriately demonstrated. This may impact on the interpretation of the process validation and comparability components of the dossier such that claims of comparability could not be fully supported at that time. The applicant was requested to provide additional data demonstrating that the current IEF method and broad acceptance limits are justified to evaluate mepolizumab charge variants.

In his response to the Day 120 Major Objection, the applicant provided a justification to continue using IEF for detection of charged variants.

The applicant provided additional IEF data on stressed samples to demonstrate the robustness of the method. According to the applicant an additional method, weak cation exchange chromatography (CIEX) was employed to provide additional understanding of these charged isoforms. Fractions from CIEX were collected and analysed by IEF. The applicant states that chromatographic fractions, which appeared homogeneous when they were re-injected on the CIEX chromatographic column, in some cases produced multiple bands on the IEF gel. According to the applicant, this would be an indication of the higher resolving power of the IEF method. However, this suggests that the IEF gel is capable of only resolving gross degradation products.

Another concern with the IEF method is the broad acceptance limits and although the applicant attempted to justify these limits, it is clear that the current acceptance limits for this method are beyond the proposed range and are therefore unacceptable. The applicant states that acceptance criteria for IEF were determined by statistical evaluation of commercial scale batch data and considers that the limits derived from IEF

accurately reflect manufacturing experience to date and will avoid needless rejection of acceptable batches in the future. From the CHMP point of view, the poor resolution of the IEF method may not allow detection of all charged variants and the wide acceptance limits of the IEF allow wide heterogeneity in the product in this respect. This is not acceptable at release, and also comparability regarding these product forms has not been satisfactorily demonstrated using the IEF technique.

Therefore, the applicant should improve the analytical method used to investigate charge variants and apply it to investigate the consistency of the production process and, where necessary, improve it.

There are also other concerns related to the unresolved issue of charged variants and they are pertaining to:
a) Identity testing;
b) Drug substance shelf life;
c) Purity evaluation of the drug substance;
d) Drug product shelf life.

For most of the Other Concerns raised at Day 120, the applicant has provided satisfactory responses. However, there are few additional issues that need further clarification and/or additional data, e.g. productivity of the MCB, validation of the intermediate hold steps, specification and validation of the bioactivity assay, process-related impurities and validation of the holding time for thawing the bulk drug substance.

3. CONCLUSION:

The CHMP endorsed the conclusions drawn by the Rapporteur and Co-Rapporteur.
Based on the review of the data on Quality, the CHMP considered that the application for Bosatria was not approvable since a Major Objection remained unresolved, which precluded a recommendation for marketing authorisation.
In addition, several other concerns still needed to be addressed by the applicant before the granting of a marketing authorisation could be recommended**.**

II.2 Non clinical aspects

Pharmacology
Mepolizumab was tested in a range of *in vitro* experiments to characterise receptor binding and species-specificity, as well as in *in vivo* studies in animal models, and in a safety pharmacology study. Mepolizumab does not crossreact with mouse, rat, guinea pig, rabbit or dog IL-5 *in vitro*, hence, the key nonclinical studies were conducted in cynomolgus monkeys. The safety pharmacology study was conducted in accordance with the GLP regulations.

Most non-clinical pharmacology studies were conducted using the humanised monoclonal antibody, mepolizumab. However, a few studies were conducted with the parent murine anti-hIL-5 monoclonal antibody (clone 2B6, which was used to generate mepolizumab), and a rat monoclonal antibody (SB-264091), directed against hIL-5, which is pharmacologically active in mice.

The receptor binding and species-specificity of mepolizumab were examined *in vitro* in a range of binding and cell proliferation assays. Binding kinetics of mepolizumab was evaluated using surface plasmon resonance (Biacore) and titration microcalorimetry. Mepolizumab has high affinity for and is specific for human IL-5 (hIL-5), but also recognises monkey IL-5. Biacore analysis showed that mepolizumab bound to IL-5 with a K_d of ≤100 pM, and with an estimated *off* rate of $1.7x10^{-5}s^{-1}$ and an *on* rate of $1.6x10^{5}M^{-1}s^{-1}$. A subsequent, more sensitive Biacore assay suggested an even higher affinity (K_d of 4.2 pM).

Stoichiometric analysis using titration microcalorimetry showed a 1:1 ratio of IL-5 to antibody and high affinity of mepolizumab for IL-5 (<130 pM at 25°C). Analytical ultracentrifugation, which measures IL-5 in its native homodimer format, showed a ratio of two mepolizumab antibodies bound to two IL-5 homodimers.

The effect of mepolizumab on binding of IL-5 to IL-5R was determined using ^{125}I-labelled IL-5 and *Drosophila* cell membranes expressing the IL-5Rα subunit. Mepolizumab inhibited binding of IL-5 to its receptor with an IC_{50} value of <1.0 nM. Similar inhibitory effect was observed for the parental hIL-5 antibody clone 2B6 and the chimeric hIL-5 monoclonal antibody IL-5CH.

The effect of mepolizumab on cell proliferation was evaluated using different human and mouse cell lines. Mepolizumab inhibited the proliferative responses of an IL-5/IL-3 dependent pre-B cell line B13, and of a human erythroleukemic cell line TF-1.28, to IL-5 with IC_{50} values of <100 pM and <150 pM, respectively. Comparable effect was observed with the parental clone 2B6 and with the chimeric antibody IL5CH. Eosinophil differentiation of human bone marrow/mononuclear cells was shown to be blocked by mepolizumab.

A comparison of the activity of mepolizumab against human and monkey IL-5 was performed in an experimental setting using *Drosophila* cells expressing recombinant human and cynomolgus monkey IL-5. The EC_{50} values as measured by the proliferative response of human TF-1.28 and mouse IL-5 receptor-positive B13 cell lines were comparable. Mepolizumab similarly inhibited the biological activity of human and monkey IL-5. However, mepolizumab proved to be pharmacologically inactive in rat, rabbit, and guinea pig.

The proof of concept was demonstrated in cynomolgus monkeys after intravenous administration of mepolizumab. In the two-months repeat-dose toxicity study, a monthly administration of ≥0.5 mg/kg of mepolizumab appeared to block by 85% the eosinophilia induced by recombinant IL-2 treatment. However, the effect of mepolizumab on the level of circulating eosinophils could not be reliably demonstrated in this study due to exceptionally low basal eosinophil levels in most of the animals at the start of the study. A clear and effective reduction of circulating eosinophil levels by mepolizumab was demonstrated in the 6-month repeat-dose toxicity study. Compared to the vehicle treated animals a monthly intravenous administration of mepolizumab ≥10 mg/kg resulted in ≥80% reduction in circulating eosinophil levels, and the effect appeared to last throughout the study duration.

Two studies were conducted with mepolizumab in an experimental model of asthma in cynomolgus monkeys. Cynomolgus monkeys exhibit a bronchoconstrictor response to inhaled *Ascaris suum* antigen, and this response is associated with prominent blood and lung eosinophilia at 24h after antigen challenge. The monkeys were treated with 10 mg/kg of mepolizumab, and challenged with *A. suum* antigen at 24 hours after dosing and at 3 and 6 weeks post dosing. Treatment with mepolizumab resulted in a marked inhibition of the bronchoalveolar lavage eosinophilia compared to vehicle treated animals at 3 and 6 weeks. Mean peripheral blood eosinophils counts were reduced approximately 50% compared to pre-study values in mepolizumab-treated monkeys, while all other haematologic parameters remained unaffected. Mepolizumab was tested together with a humanised anti-IL-4 monoclonal antibody in a similar experimental setting in the monkey asthma model. Results were consistent with the findings with mepolizumab alone, no additional value of the combination of the two monoclonal antibodies could be seen.

Pharmacodynamic/pharmacokinetic relationship was evaluated in cynomolgus monkeys. The monkeys received a single intravenous dose of 1 mg/kg mepolizumab followed by a subcutaneous dose of 1 mg/kg 3 months later. Mepolizumab plasma levels and eosinophil counts were followed for 13 weeks post dosing. The results revealed a time delay in the manifestation of maximal effect on basal eosinophil count. The maximum percent increase (81% to 96%) relative to baseline was observed at three weeks post-dosing, whilst maximal concentrations were observed at 2 to 4 days post-dosing.

The pharmacological activity, pharmacokinetics and antigenicity of SB-264091, a rat monoclonal antibody directed against hIL-5, was assessed in mice. SB-264091 proved to be pharmacologically active in mice, and there was no significant effect on total leukocyte counts or red cell measurements. Anti-SB-264091 antibodies were detected in some animals. These antibodies seem to affect the PK of SB-264091 as the plasma levels appeared to be significantly reduced in the samples from animals with anti-SB-264091 antibodies. Pharmacological activity was measured from different animals and thus, direct relationship between the occurrence of the antibodies and eosinophil count can not be assessed.

Eosinophils play a role in parasite immune response and therefore, the effect of an IL-5 antibody on host defense was evaluated using the rat anti hIL-5 mAb SB-264091 in mice infected with a parasite *Mesocestoides corti*. Consistent with the predicted pharmacologic activity, SB-264091 treatment significantly reduced the eosinophilia response to ***M. corti*** infection but had no significant effects on other aspects of the inflammatory responses, parasite burden, or survival, indicating that host defense was not impaired by treatment with SB-264091. It seems that the pharmacological effect of SB-264091 is not affected by possible occurrence of anti-SB-264091 antibodies. This gives assurance to a certain extent that the homologous system using rat mAb against hIL-5 in developmental and reproductive toxicity testing is justifiable.

No formal secondary pharmacology studies were conducted with mepolizumab. Mepolizumab would not be expected to bind to cell surfaces because IL-5 is a soluble cytokine. This is supported by tissue binding data that demonstrated intracellular binding to lymphoid tissues only. In addition, mepolizumab is not capable of binding to IL-5 when bound to the receptor, as mepolizumab competitively blocks binding of IL-5 to the IL-5 receptor alpha chain. Therefore, the possibility of effector functions through the Fc region of the antibody is anticipated to be very low.

A safety pharmacology study was performed to evaluate the effects of mepolizumab on respiratory, cardiovascular and renal systems. Central and peripheral nervous system parameters were not evaluated. There were no significant effects on any of the parameters tested that could be attributed to mepolizumab. Statistically significant differences in blood pressure were noted between the vehicle and mepolizumab treated animals. The effect was interpreted to be unrelated to treatment because the results with the second vehicle treatment were within the range of those obtained with mepolizumab. However, and partially due to low number of animals (three males), this possibility can not be excluded.

No studies have been conducted on the pharmacodynamic drug interactions of mepolizumab. However, the HES patients usually receive other concomitant medication, such as corticosteroids. The applicant discussed the potential effects of using immunosuppressive treatments in combination with mepolizumab, and based on that it is unlikely that mepolizumab would significantly add risk of immunosuppression when used in combination with other immunosuppressants.

Pharmacokinetics

The nonclinical pharmacokinetic properties of mepolizumab have largely been investigated in the cynomolgus monkey in the toxicity studies at doses up to 100 mg/kg. Because mepolizumab is a monoclonal antibody, conventional studies of distribution, metabolism and excretion have not been conducted.

In mice, the single-dose PK variables Cmax and AUC were dose-proportional. T1/2 and Vss were rather independent on dose with slow elimination of about 5 days. In rats given humanized anti-IL-5 antibody 1mg/kg, the pharmacokinetics was comparable to that of other humanized IgG1 class monoclonal antibodies. In monkeys, the single-dose PK variables Cmax and AUC were dose-proportional and $T_{1/2}$ and Vss were rather independent on dose with slow elimination of about 12 days. In monkeys, the multiple-dose PK variables Cmax and AUC were dose-proportional and $T_{1/2}$ and Vss were rather independent on

dose with slow elimination of about 13 days. Mepolizumab concentration in alveoli was 1/500 of that found in plasma during the 6-months toxicity study. Plasma concentrations were analyzed in 3 monkeys after single inhalation dose. This method of administration was associated with anti-mepolizumab antibody development in 2 monkeys leading to low bioavailability and $T_{1/2}$ could not be determined. In one monkey that did not develop anti-mepolizumab antibodies $T_{1/2}$ was the same as in other studies after IV administration.

The pharmacokinetics of the two materials used in Phase I/II and Phase III studies are comparable in monkeys. However, the commercial scale (5000l) material has not been compared in these studies. The pharmacokinetics of the two differently glycosylated commercial scale lots are comparable.

Mepolizumab concentrations were 1.24-2.46 times higher in plasma of infants born to mothers given mepolizumab 10 and 100mg/kg than in the plasma of mothers. After 6 months, there were still detectable concentrations in plasma after the higher dose. The effects on the maturation of immune system and long term symptoms in infants and children are not known. Excretion of mepolizumab into maternal milk is very low and is not plausible to cause clinical problems, because mepolizumab is not absorbed from gastrointestinal tract.

In general, pharmacokinetic analyses indicated that mepolizumab exposure was not limited by development of immune antibody responses. There was a modest anti-mepolizumab antibody response with antibodies detected in one female monkey and her infant in the pre-and post-natal development study and in one monkey in a pharmacokinetic study assessing the comparability of drug product following manufacturing changes. Formation of anti-mepolizumab antibodies was accompanied by a faster clearance of mepolizumab from systemic circulation and also by a lower decrease in eosinophil counts.

In a study in mice using SB-264091, a homologous anti-IL-5 monoclonal antibody to mepolizumab that is pharmacologically active in rodents, plasma concentrations increased with increasing dose from 5 to 50 mg/kg and were quantifiable over the 29-day sampling period. Considerable inter-animal variability was observed and the majority of these differences could be attributed to the presence of anti-SB-264091 antibodies.

Toxicology

The applicant has conducted an abbreviated toxicity programme with mepolizumab, in only one species, the cynomolgus monkey, and at two doses in the pivotal studies. The choice of the cynomolgus monkey was justified on the basis of cross-reactivity with monkey IL-5. It is accepted that other standard laboratory species would not have been suitable and that the doses chosen for the pivotal toxicity studies were adequate. Toxicity of mepolizumab was evaluated in a series of studies in cynomolgus monkeys. A reproductive and developmental toxicity study was conducted in mice with SB-264091, a homologous rat anti-human IL-5 monoclonal antibody that is pharmacologically active in mice. The definitive toxicology studies conducted with mepolizumab and SB-264091 were performed in compliance with the GLP regulations.

Single-dose toxicity was investigated in cynomolgus monkeys (1M+1F/group) after intravenous administration of mepolizumab at dose levels of 3 and 304 mg/kg, the high dose being the maximum feasible dose limited by volume. Doses up to 304 mg/kg were well tolerated over a one-month observation period. There were no meaningful treatment-related in-life or histopathological findings.

Repeat-dose toxicity of mepolizumab was evaluated in two studies in cynomolgus monkeys. In the two-month study, two monthly intravenous doses of mepolizumab at the dose levels of 0.05, 0.5, 5 or 50 mg/kg were administered to groups (2M+2F/group) of monkeys. Mepolizumab appeared to be well tolerated over the 13-week observation period. The principal effect observed in toxicology studies of up to

6 months' duration was related to the pharmacology of the drug and was reversible following the cessation of treatment. The NOAEL for monkeys in the 6 month study was >100 mg/kg with a mean Cmax of 2.4 mg/mL and AUC of 809 mg.h/mL. In the six-month study, seven intravenous doses of 10 and 100 mg/kg and subcutaneous doses of 10 mg/kg were administered monthly to cynomolgus monkeys (3M+3F/group). With the exception of the expected decrease in eosinophil counts, there were no meaningful treatment-related effects. Histological evaluation of the subcutaneous injection sites revealed minor injection-related trauma. None of the mepolizumab-treated monkeys generated anti-mepolizumab antibodies following repeated intravenous or subcutaneous dosing.

Toxicokinetics was evaluated in the single and repeat dose studies. In all studies, systemic exposure was approximately dose proportional and there were no marked differences between male and female monkeys. The terminal half-life was approximately 13 days. In the six-month repeat dose study, trough plasma concentrations reached the plateau after the fourth monthly dose. The exposure in monkeys represents a 9.7-fold multiple of the human exposure.

In line with the ICH S6 guideline, genotoxicity testing was considered unnecessary. Carcinogenicity testing was considered unnecessary due to the fact that as a monoclonal antibody, mepolizumab is not believed to possess an inherent carcinogenic potential.

Evaluation of effects of mepolizumab on fertility and embryo-fetal development was performed in a homologous model in mice using SB-264091, a rat anti-human IL-5 monoclonal antibody that is pharmacologically active in mice. Weekly administration of SB-264091 to male and female mice at dose levels of 0.5 and 50 mg/kg was not associated with effects on mating, fertility and gonadal function or on early embryonic or embryo-fetal development. Comparable exposure of the females to the surrogate antibody was ensured by more frequent dosing. It is accepted that this study does not provide direct information for the risk assessment of mepolizumab, but does provide supporting evidence that blockade of IL-5 does not appear to have any effects on fertility and fetal morphology in mice. The NOAEL was >50 mg/kg.

In the monkey pre- and post-natal development study, monthly intravenous administration of up to 100 mg/kg of mepolizumab during gestation did not result in maternal toxicity, nor was it associated with significant effects on pregnancy outcome or delivery, or effects on fetal development. Effects on general health or immunologic development of offspring evaluated for nine months post-partum were not noted. Significant concentrations of mepolizumab were present in the circulation of the offspring for up to 6 months postpartum as a result of transplacental transfer from the dosed mothers. Toxicokinetic analysis of the pre-and postnatal study confirmed exposure of the monkeys to sustained serum concentrations of mepolizumab, but only the higher dose provided exposure greater than that in humans with a safety margin of 4.3. The NOAELs for adults and offspring were both >100 mg/kg with a mean Cmax of 1.159 mg/ml and an AUC of 254.1 mg.h/ml in the adults. Concentrations in the infants were around 2.4 times those in adults. Mepolizumab was detected in maternal milk at the 100 mg/kg dose at levels comparable to 0.5% of the levels in maternal plasma. Due to the fact that monkey and human placentas are similar, transfer of mepolizumab would be expected to occur during the last trimester of pregnancy in human situation. Excretion to milk would also be expected for humans. Due to limited number of animals used in this study and the limitations of the homologous mouse model, reproductive and developmental toxicity data is considered limited. Therefore, use of mepolizumab during pregnancy and lactation can not be recommended.

Local tolerance was evaluated only with subcutaneous route. Subcutaneous dosing was associated with mild injection site reactions most likely due to injection trauma.

Immunogenicity of mepolizumab was tested in a set of toxicity studies using appropriately validated assays. Anti-mepolizumab antibodies were detected in only 3% of animals. However, occurrence of anti-

mepolizumab antibodies was associated with enhanced systemic clearance of mepolizumab and reduced pharmacological activity in terms of circulating eosinophil levels.

The potential for mepolizumab-mediated immunotoxicity was evaluated in toxicology studies. Reduced eosinophil counts were observed, but there were no mepolizumab-related effects on lymphocyte immunophenotyping in monkeys. Furthermore, in the pre-/post-natal study in monkeys, infants of mothers treated with mepolizumab had normal responses to Tripedia vaccine. Results with SB-264091, a rat anti-human IL-5 monoclonal antibody surrogate, indicate that IL-5 antibody has no effect on parasite burden in a murine host defense model using *M. corti* as the pathogen. Tumors were not observed in any of the preclinical studies. However, in clinical studies a number of malignancies were seen, some of which were considered treatment-related. Many of the monkeys used in single and repeat-dose toxicity studies appeared to suffer from bacterial infections or parasites during the course of the study. The cynomolgus monkey stock was not standardised at that time and this could partially explain the relatively high occurrence of infections. However, it is not possible to exclude the possibility of increased incidence of infections in mepolizumab-treated monkeys. Increased incidence of infections in mepolizumab-treated patients was observed.

Immunohistological tissue binding study with human tissues showed that mepolizumab was almost exclusively bound to lymphoid tissues, such as bone marrow, spleen, lymph node and tonsil. Weak staining of inflammatory cells in one specimen of the prostate was also observed. Therefore, pharmacological effects beyond the immune system are not anticipated.

The level of the main impurity, an aggregate, has not been qualified in the toxicity studies. The applicant should provide qualification data in line with the Note for Guidance ICH Q3B, Impurities in New Drug Substances (qualification threshold for impurities in New Drug Products for a dose >100 mg – 2 g = 0.2%).

Because mepolizumab is a protein, an environmental risk assessment is not considered necessary.

The applicant has conducted an acceptable programme of toxicity studies. Only two dose levels of mepolizumab have been studied and mostly only one species for the toxicology, but this is acceptable for this type of product. The duration of the repeat-dose studies is adequate to support a marketing authorisation and there is no need for any more studies of any type to be conducted.

II.3 Clinical aspects

Pharmacokinetics

The pharmacokinetics of mepolizumab have been evaluated in seven studies (five Phase I, one Phase II, and one Phase III). The pharmacokinetic profile of mepolizumab has been well characterised in healthy volunteers but mostly in patients with asthma and in the target population. Doses of 0.05 to 10 mg/kg have been administered as well as flat doses of 250 and 750 mg.

These studies involved 143 subjects in the 5 Phase I studies (110 active, 33 placebo). In addition, there were 429 subjects in the Phase II studies (267 active, 162 placebo), and 85 HES subjects in the Phase III study (43 active and 42 placebo).

The pharmacology studies of mepolizumab (11) are summarised in **Table 1**.

Table 1 Summary of all pharmacology studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects/total exposed to mepolizumab
Biopharmaceutic Studies					
SB-240563/018 (RSD-101TLH/1)	Bioavailability and safety	R, OL, PG	Healthy volunteers	Mepolizumab 250 mg SC abdomen, arm or thigh; single dose Mepolizumab 250 mg IM; single dose Mepolizumab 250 mg IV; single dose	60//60
Pharmacokinetic Studies					
SB-240563/001 (RSD-100MF5/1)	Safety, PK, and PD	R, DB, PC, DR	Mild asthma (males only)	Mepolizumab 0.05, 0.5, 2.5, 10 mg/kg IV; single dose Placebo IV; single dose	38/25
SB-240563/035 (RSD-100M42/1)	Safety, PK and PD	R, DB, PC, DR	Mild asthma (males only)	Mepolizumab 0.5, 2.5, 10 mg/kg IV; single dose Placebo IV; single dose	18/12
SB-240563/017 (RSD-10173B/1)	Tolerability and PK	R, DB, PC, PG	Asthma	Mepolizumab 250 mg SC Placebo SC Three doses: Weeks 1, 6, and 8	16/8
Efficacy and Safety Studies: Controlled Clinical Studies Pertinent to the Claimed Indication					
MHE100185 (UM2004/00091/01)	Efficacy and safety; PK analysis	R, DB, PC, PG	HES	Mepolizumab 750 mg IV Placebo IV One infusion per month for 9 months	85/43
Asthma					
SB-240563/006 (SB-240563/RSD-1016KH/1)	Efficacy and safety; PK analysis	R, DB, PC, PG	Asthma	Mepolizumab 250 mg IV Mepolizumab 750 mg IV Placebo IV One infusion per month for 3 months.	362/236
SB-240563/036 (RSD-101TDT/1)	PD and safety	R, DB, PC, PG	Atopic asthma	Mepolizumab 750 mg IV Placebo IV One infusion per month for 3 months	24/11
Atopic Dermatitis					
SB-240563/045 (RSD-101XFC/1)	Efficacy, PD and safety	R, DB, PC, PG	Atopic dermatitis	Mepolizumab 750 mg IV Placebo IV Two infusions given 1 week apart.	43/20
Eosinophilic Esophagitis					
MEE103226 (GM2007/00041/00)	Efficacy and safety; PK analysis	R, DB, PC	EE (adult)	Mepolizumab 750 mg and 1500 mg IV Placebo IV Once infusion every 4 weeks for 13 weeks	11/5

CPSR = Clinical Pharmacology Study Report
DB = Double-blind
DR = Dose ranging
EE = Eosinophilic Esophagitis
EU = European Union
HES = Hypereosinophilic Syndrome
IM = intramuscular
IV = intravenous
OL = Open label
PC = Placebo-controlled
PD = Pharmacodynamics
PG = Parallel group
PK = Pharmacokinetic
R = Randomized
ROW = Rest of World
SC = subcutaneous
UK - United Kingdom
USA = United States of America

Pharmacokinetic profile

A two-compartment model with first-order elimination best described the plasma concentration-time profile of mepolizumab. The maximum concentration is reached within 4 hours after IV dosing. In monkeys and in humans mepolizumab exhibits dose-proportional pharmacokinetics AUC and Cmax increasing proportional to dose. In multidose-studies, mepolizumab plasma concentrations have been similar to values predicted using data from single-dose studies. Full and sparse sampling across all studies indicates that mepolizumab exhibits time-independent pharmacokinetics and first-order elimination kinetics.

- Absorption

Intramuscular and subcutaneous absorption of mepolizumab was slow (over 4 days). The absorption of SC dose was even slower after repeated dosing in 4 out of the 7 subjects. The bioavailability was better after IM administration compared to SC administration irrespective of the site of SC dose. IV-administration is the proposed method of administration of mepolizumab in HES.

- Bioequivalence

The bioequivalence of the two drug products used in clinical trials (180l scale vs. 1200l scale) has been confirmed in a separate study of 10 cynomolgus monkeys. However, the bioequivalence of the commercial scale drug product (5000l) has not been compared with the 1200L scale drug product used in the pivotal HES study.

- Distribution

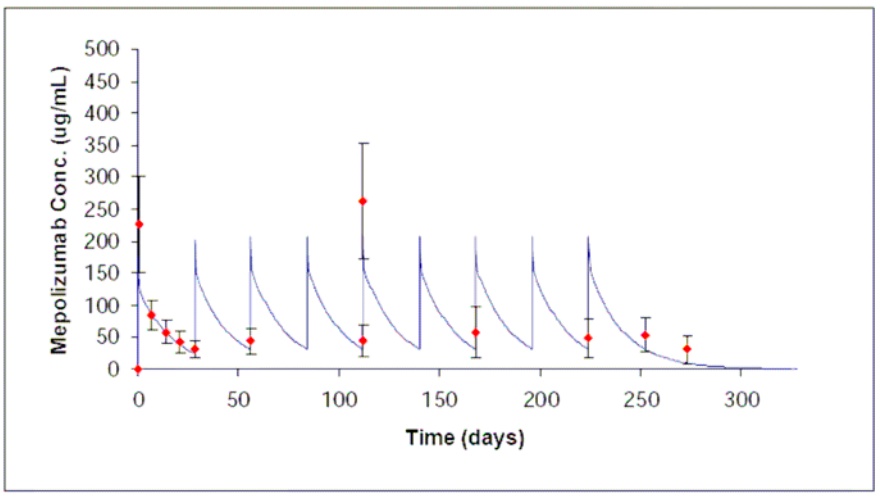
Vc was similar to plasma volume and Vss was about 1.5 to 2 times plasma volume.

Binding of mepolizumab to fixed human tissues has been evaluated with immunocytochemical analysis using biotinylated-mepolizumab and DAB. Immunoreactivity was observed in cells of the granulocytic series in the bone marrow, lymph node, in the red pulp, reticuloendothelial cells and white pulp of the spleen, in lymphoid cells in the perifollicular region of the tonsil and in dendritic cells in the submucosa, germinal centers, and intraepithelial and in inflammatory cells in one specimen of the prostate. The binding of mepolizumab to red blood cells is not known. In studies with monkeys, mepolizumab concentration in alveoli was 1/500 of that found in plasma.

- Elimination

The elimination of mepolizumab is slow, mean terminal $T_{1/2}$ being 18.5 to 21.7 days and Cl 0.081 to 0.137 ml/h/kg after single doses. No unexpected accumulation can be identified after repeated IV dosing of 250mg or 750 mg of mepolizumab when sparse samples were taken before and after dosing. At the recommended posology (750 mg monthly), trough levels are maintained at an average 30-50 µg/ml in the target population (see **Figure 1**).

Figure 1 Mean (SD) observed mepolizumab plasma concentrations and predicted profiles (Study MHE100185)



Transfer of mepolizumab to milk in nursing monkeys was detected 2-4 weeks after 100mg/kg dose. The concentration of mebolizumab was under 0.5% in milk compared to plasma concentration measured at the same day.

It is not plausible that renal function would affect elimination of mepolizumab. The applicant has clarified the concentrations of mebolizumab of the subjects with renal impairment in the pivotal HES study relative to mean plasma concentration of all subjects.

Special populations

- Inevitably, data are limited in most special subpopulations (impaired renal or hepatic function, other race than Caucasian, elderly, children) given the rarity of the disease.
- In the final population pharmacokinetic model, weight was identified as a statistically significant covariate for the clearance and central volume of distribution. In view of the broad range of weight reported in the target population of the pivotal trial, the applicant should reconsider their rationale for administering a flat dose of mepolizumab.
- The drug should be used with caution during pregnancy, since it crossed the placenta readily in monkeys and high (2.4 times higher than in nursing mothers) concentrations were developed in infants.

Interactions

- There does not seem to be any obvious interaction between the type of disease or the corticosteroid therapy and the pharmacokinetics of mepolizumab.
- Likewise, the absence of data on the combination of Bosatria with other therapies administered in HES, including interferon alpha, hydroxyurea, immunosuppressants and imatinib, should be included in the SmPC

Pharmacodynamics

The pharmacodynamics of mepolizumab have been evaluated in seven studies:

- three of the Phase I studies, including two single-dose, placebo-controlled, dose-rising studies in subjects with mild-to-moderate asthma (**Study SB-240563/001** and **Study SB-240563/035**) and a multiple-dose, placebo-controlled study in subjects with EE (**Study MEE103226**);

- two phase II studies, where only the safety and pharmacodynamics of mepolizumab were evaluated: **Study SB-240563/036** in subjects with atopic asthma and **Study SB-240563/045** in subjects with atopic dermatitis (AD);
- the Phase III **Study MHE100185**, a randomised, double-blind, placebo-controlled study in subjects with HES;
- the Phase II **Study SB-240564/006**, a randomised, double-blind, placebo-controlled study in subjects with asthma.

Mechanism of action

By binding to free IL-5 with high specificity and affinity, mepolizumab prevents IL-5 from associating with the IL-5 receptor on the surface of eosinophils and their progenitors. Inhibition of IL-5 signalling leads to decreases in the accumulation and activation of circulating eosinophils in the blood. However, the binding of mepolizumab to IL-5 has not been characterised at the molecular level. Immunocytochemical data on the binding of mepolizumab to a panel of normal human tissue has shown equivocal results. The applicant has noted that there was no staining on the surface of peripheral blood leukocytes in the IHC study, but has not addressed the question of whether this is representative of what happens when mepolizumab is dosed to humans *in vivo*.

Preclinical studies have indicated that blocking IL-5 will result in reduction of peripheral eosinophil count in blood and some tissues. Blood eosinophil count has been shown to be a good biomarker to study pharmacological response of mepolizumab. In addition to regulating eosinophils, IL-5 takes part also in B-cell development and immunoglobulin production. Blocking action of IL-5 may potentially lead to changes in B-cell functions and immunological abnormalities in bacterial and viral defence. The potential for latent infection activation when using mepolizumab has been also addressed in the risk management plan. The applicant commits to employ a systematic and pro-active process for identifying safety signals and will continue to monitor for any possible association between mepolizumab and the development of PML.

Effect on peripheral blood eosinophil count

The effect of mepolizumab on peripheral blood eosinophils is well documented. Doses above 0.5 mg/kg mepolizumab decrease blood eosinophil count ~80% from baseline to below 100/µl, with increases back up toward baseline levels after approximately 60 days for a 2.5 mg/kg dose, and after more than 80 days for the 10 mg/kg dose. While it is dose-dependant over the range of 0.5 to 10 mg/kg when administered at a single dose (see **Figure 2**), there is no difference between multiple monthly dosing at 250 or 750 mg (approximately 80% reduction at least up to 8 weeks following the last dose) (see **Figure 3**). Besides, an estimate of IC50 produced by PK/PD modelling would also suggest that monthly dosing at 250 mg could be sufficient. The applicant should further justify their rationale for selecting 750 mg monthly as the dose to be tested in the pivotal in HES.

Figure 2 Mean (+SD) Eosinophil Count vs. time profiles (Study SB-240563/035)

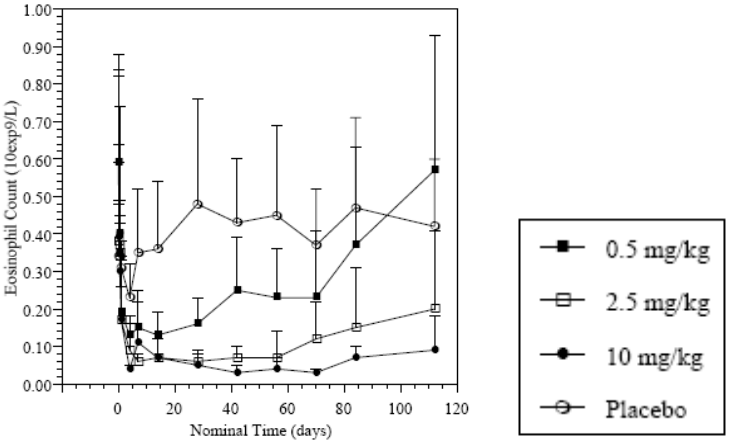
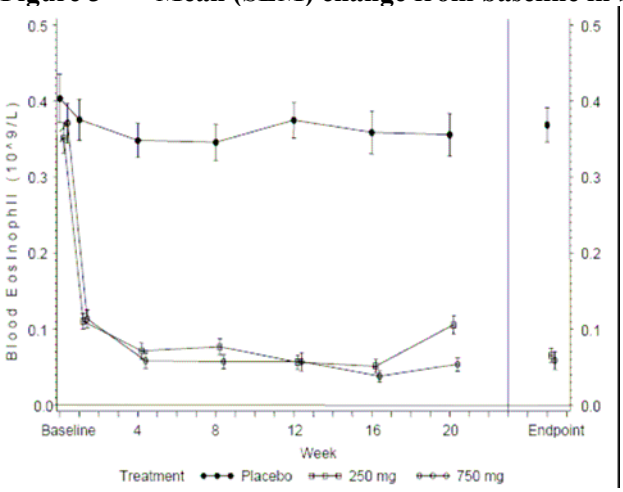


Figure 3 Mean (SEM) change from baseline in blood eosinophil count (SB-240563/006)



In the pivotal HES study MHE100185, blood eosinophil count <600 cells/µl for a period of at least eight consecutive weeks was used as a secondary endpoint during mepolizumab 750mg IV once monthly for 9 months. Sustained reduction of eosinophil count <600 cells/µl for a period of at least eight consecutive weeks was reached in 95% of HES patients with mepolizumab 750mg IV compared to 45% of HES patients treated with placebo.

Blood eosinophils were reduced maximally also by 4-5 weeks in a study with EE patients given mepolizumab two 750mg IV doses at 1 week's interval. Additional doses of 1500mg were given at wk 4 and wk 9 in this study and the eosinophil counts were still low after 16 wks following the last dose of mepolizumab.

The population PK/PD analysis did not give further information on concentration-effect relationship since most of the data came from study SB-240563/006 where all mepolizumab patients had a highly variable effect from the two doses given (250mg and 750mg).

IL-5 concentrations were increased by mepolizumab treatment in the pivotal HES study MHE100185. In study SB-240563/001, IL-5 in blood was increased by mepolizumab on day 29 post dosing at the 2.5 mg/kg dose.

Effect on tissue/fluid eosinophil counts

In study SB-240563/036 eosinophil counts in tissues and fluids were evaluated in skin, bone marrow, nasal lavage fluid, and bronchial mucosa in patients with atopic asthma following three monthly 750mg IV infusions of mepolizumab but mepolizumab concentrations were not measured in this study. Significant reductions in eosinophil counts in tissues and fluids were observed in skin, bone marrow, nasal lavage fluid, and bronchial mucosa in patients with atopic asthma. This effect appears much less dramatic and less consistent than in peripheral blood where it is considered clinically more relevant. Although supportive, literature data in HES are not considered sufficient; data on the effect of mepolizumab on tissue infiltration by eosinophils in the claimed indication should be provided.

Clinical efficacy

The data which support the efficacy of mepolizumab in HES are provided from two clinical trials (pivotal study MHE100185 and the open-label extension of this study, MHE100901) and from the Compassionate Use Program.

The dossier contains one pivotal randomized, double-blind placebo-controlled trial in the proposed indication with 85 HES patients. One pivotal study was accepted by CHMP SAWP for this orphan drug indication. The patients from this pivotal study were recruited to open-label extension study, where all patients received mepolizumab and the primary objective was to evaluate long term safety. Studies in paediatric or special populations have not been performed.

The studies relevant to HES are summarised in **Table 2**.

Table 2 Summary of the studies in HES

Study Identifier	Study Objective(s)	Study Design	Indication	Treatment Details	Total No. of Patients
MHE100185	Efficacy and safety; PK analysis	Randomised, Double-blind, Placebo controlled	HES	Mepolizumab 750 mg IV - Monthly infusions x 9	85
MHE100901 - Extension of ME100185	Long-term safety	Open label	HES	Mepolizumab 750 mg IV; timing of dosing dependent on blood eosinophil count and clinical presentation	78
Initial Compassionate Use 2001-2003	Compassionate use	Open label	Hypereosinophilia	Mepolizumab 250 mg - 1300 mg IV, at variable intervals	15
MHE104317	Compassionate use (USA)	Open label	HES	Mepolizumab - monthly IV infusions up to 10 mg/kg (max dose 750 mg or 10 mg/kg if body weight <45 kg) for an initial 3 months of treatment- Subsequent treatment dosing frequency determined by eosinophil level and/or clinical presentation	31
Named Patient Supply Program	Compassionate use (EU and ROW)	Open label	HES		29

<u>Pivotal Study MHE100185:</u> A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Phase III Study to Evaluate Corticosteroid reduction and -sparing Effects of Mepolizumab 750mg Intravenously in Subjects with Hypereosinophilic Syndrome (HES), and to Evaluate the Efficacy and Safety of Mepolizumab in Controlling the Clinical Signs and Symptoms of HES over Nine Months

- **Study Participants**

This was a randomised placebo-controlled study comparing the addition of mepolizumab or placebo to prednisone therapy in patients whose clinical symptoms were stabilised with the use of prednisone monotherapy (20 to 60 mg/day). It was conducted from March 2004 to March 2006 in 26 centres: 11 in the USA (46% of the patients), 9 in the EU (3 in Belgium, 3 in Germany, 2 in France and one in Italy), 4 in Canada, and 2 in Australia.

Eligible subjects were:

- males and females, 18 to 85 years of age
- with a documented history of HES: peripheral blood eosinophils >1500 cells/μl for at least 6 months and signs/symptoms of organ system involvement or dysfunction directly related to eosinophilia and no evidence of parasitic, allergic, or other recognised causes of eosinophilia after comprehensive evaluation
- with a negative test for the presence of the FIP1-PGFRAα fusion gene
- with a stable prednisone monotherapy status prior to randomization, as reflected by a blood eosinophil count <1000 cells/μl with no new or worsening HES signs/symptoms on ≥20 mg to ≤60 mg once daily for at least 1 week.

The selection criteria were mostly in line with the CHMP advice. Subjects that tested positive for FIP1L1-PDGFRα fusion gene were excluded from the study population, since they usually have a more aggressive myeloproliferative disease and develop acute myelogenous eosinophilic leukaemia. However, the myeloproliferative variant form of the disease can on occasion be associated with FIP1 negative status. CHMP proposed that for determining the target populations to perform a bone marrow biopsy and cytogenetic analysis on bone marrow aspiration, to better differentiate myeloproliferative from non-myeloproliferative variant of the disease. However, a bone marrow biopsy and cytogenic analysis on bone marrow aspiration were not included in target population determination. The applicant has justified that bone marrow specimens were not analysed as differential diagnosis could be performed with less invasive diagnostic testing and would not be needed before treatment with mepolizumab for the applied indication

- **Treatments**

The study comprised a Screening Visit, a prednisone run-in and stabilization period, a Baseline Visit, a Treatment Period of 36 weeks and a Safety Follow Up (FU) Visit. After the initial screening, subjects washout all the other HES medications, switch to prednisone and/or adjust their prednisone dose in order to achieve a stable prednisone monotherapy status. The Treatment Period commenced at Day 1 after randomization and completed at Week 36. Central randomization was applied using randomly permuted blocks within two strata based upon subjects' stable entry prednisone daily doses of ≤ 30 mg or >30 mg. Subjects in each strata were randomized at 1:1 ratio to receive either 750 mg mepolizumab IV infusion, or saline (as placebo) IV infusion every 4 weeks beginning from Day 1 until the last infusion at Week 32. Weekly prednisone taper started one week after the first dose following the Prednisone Taper Schedule. The maximum total study duration for a participating subject was 51 weeks.

The infusion solution, either mepolizumab 750 mg or saline, was administered over approximately 30 minutes once every 4 weeks beginning at Day 1 after randomisation until the last dose at Week 32, i.e. a total of 9 infusions. Patients received their infusions in the clinic. No other treatment for HES was permitted than prednisone (or equivalent). After screening, patients entered a run-in period of up to 6 weeks, during which all other treatments had to be discontinued and prednisone monotherapy was administered to achieve a stable clinical status as previously defined. Starting one week after the first infusion of the tested drug, prednisone taper followed a predefined weekly schedule. Unblinded blood eosinophil counts were provided to investigators throughout the study since this was essential to guide disease management and the steroid tapering schedule in accordance with predefined guidelines. Therefore, it is not possible to consider this trial as fully blinded for the investigator.

The choice of the dose and dosing interval for the pivotal Phase III trial is acceptable, since although both 750mg and 250mg IV gave almost similar response in reducing the eosinophil count in blood, the duration

of effect was dependent on dose and there were no evident safety concerns at higher doses, although bordeline QTc prologations were observed with this dosages in study SB-240563/006 with 362 asthma patients.

- **Objectives**

The primary endpoint was the proportion of subjects who achieved a total daily prednisone dose of ≤10mg for a period of 8 consecutive weeks. The primary endpoint has been discussed with CHMP and agreed.
The following secondary endpoints were analyzed in a hierarchical manner for statistical differences between the placebo and mepolizumab treatment groups: **1.** Proportion of subjects who maintained a blood eosinophil count of <600/µl for a period of 8 consecutive weeks during the Treatment Period. **2.** Time until treatment failure with treatment failure defined as clinical worsening requiring other HES based therapy or an increase of prednisone dose to >60mg/day per discretion of the investigator, or withdrawal from the study for any reason. **3.** Proportion of subjects who achieved a total daily prednisone dose of ≤7.5mg (sub-adrenal threshold) during the Treatment Period. **4**. Proportion of subjects who were corticosteroid-free during the Treatment Period. **5**. Mean total daily dose of prednisone. **6.** Component analysis of QoL and current health status: improvement to physical summary score analysis of the SF-12v2. **7.** Component analysis of QoL and current health status: improvement to mental summary score analysis of the SF-12v2. **8.** Proportion of subjects who achieved a total daily prednisone dose of ≤10mg within 20 weeks and who maintained a total daily prednisone dose of ≤10mg for a period of 8 consecutive weeks. **9.** Proportion of subjects who achieved total prednisone daily doses 12 weeks after randomization in the following categories: 0mg, 2.5-7.5mg, 10mg and >10mg, respectively.**10.** Pruritus visual analogue scale (pVAS). **11.** Erythema/oedema score.

It was the opinion of CHMP that end-organ involvement should be a key secondary endpoint. The protocol has only skin-related secondary end-organ endpoints. The applicant has not adequately clarified why these were not included as secondary endpoints.

Sample size

The study was powered to demonstrate a clinically meaningful difference between mepolizumab and placebo in the proportions of subjects achieving a daily prednisone dose of ≤10mg for at least 8 consecutive weeks. It was assumed that a 33% increase in responders in mepolizumab group compared to placebo would be of clinically meaningful effect.

Analysis populations

The ITT set consisted of all randomized subjects who received at least one dose of study medication. The ITT population was used in the primary analyses. The PP Population would only be analyzed if this population comprised from 50 to 90% of the ITT Population.
The PP population was not analysed, since it comprised over 90% of the ITT population.

Statistical Methods

The statistical methods are appropriate and generally used for a stratified, parallel group design.

Results

Patient disposition and baseline characteristics

A total of 107 subjects with HES were screened and 85 were randomized to treatment (42 to placebo and 43 to mepolizumab. Of the 22 screen failures, most (77%) were due to not fulfilling eligibility criteria for randomization. Demographics were generally comparable between the treatment groups. The majority of subjects were White (85%), >45 years of age (59%) (mean age 48 years), and received ≤30mg prednisone/day at baseline (71%). Overall the distribution of sex was balanced; however there was a greater proportion of males in the mepolizumab group (60%) compared with the placebo group (40%). Most subjects (73%) had HES ≤5 years; 39% of subjects had HES for ≤1 year. Mean duration of the disease was greater in the placebo group (6.5 years) compared with the mepolizumab group (4.3 years). The mean age at onset was 43 years. The most prominent current HES-related conditions included

skin/subcutaneous tissue disorders (47%) and respiratory disorders (41%). The incidence of skin disorders was higher in the placebo group (57%) than in the mepolizumab group (37%). While the mepolizumab groups were generally comparable across regions patients in the NA placebo group were likely to be more severe than those in the ROW placebo group as reflected by baseline prednisone dose, incidence of prior HES therapies and HES-related medical conditions.

The majority of subjects randomized to the mepolizumab group (84%) completed the study, whereas the majority of subjects in the placebo group (64%) withdrew, primarily due to lack of efficacy (50% of subjects). More than half of the subjects in the placebo group (55%) were from the USA, while only 37% of subjects in the mepolizumab group were from the USA. Since significant number of patients discontinued the intervention in the pivotal study (n=24; 40% of patients), the applicant should clarify if the signs and symptoms of HES leading to withdrawal due to lack of efficacy were similar in RoW and NA.

The patient disposition by region is shown in **Table 3**.

Table 3 Summary of patient disposition

	Number (%) of Subjects			
	North America		Rest of the World	
Subject Disposition	Placebo N=29	Mepolizumab 750mg N=21	Placebo N=13	Mepolizumab 750mg N=22
Status				
Completed	7 (24)	17 (81)	8 (62)	19 (86)
Withdrawn	22 (76)	4 (19)	5 (38)	3 (14)
Reason for WD				
Lack of Efficacy	18 (62)	2 (10)	3 (23)	3 (14)
Adverse event	1 (3)	1 (5)	1 (8)	0
Consent WD	1 (3)	1 (5)	0	0
Disease Progess	0	0	1 (8)	0
Other	2 (7)	0	0	0

Primary endpoint

The proportion of responders for the primary endpoint was almost two-fold greater in the mepolizumab group (84%) compared with the placebo group (43%) and this difference was statistically significant. Statistically significant differences were also observed in the proportion of responders between mepolizumab and placebo in the two baseline prednisone dose subgroups, with the difference being greater in the >30mg subgroup (**Table 4**). In the analysis of primary endpoint, the Breslow-Day test did not reveal a statistically significant treatment by baseline prednisone dose level interaction. However, the proportion of responders was similar with mepolizumab and placebo in RoW (**Table 5**).

The difference between the primary response rate (84% vs. 43%) was essentially due to the differential withdrawal rate between placebo (23/24 non responders) and mepolizumab (4/7 non responders), because in this analysis, all withdrawals before the primary endpoint was achieved were assumed to be non responders (see **Table 4**). However, the trial cannot be considered fully blinded since the investigator had access to blood eosinophil counts in order to adjust the prednisone tapering and might have been keen to enrol patients into the open label extension of the trial after withdrawal from the controlled trial. Therefore, this 'missing as failure' analysis has the potential to be highly biased in favour of mepolizumab. The applicant has not provided any evidence that these withdrawals were actually due to lack of efficacy in compliance with the protocol guidelines on prednisone taper and rescue. In the absence of detailed and documented information on the reason for each individual withdrawal from the study, the

results of the primary 'missing as failure' analysis cannot provide a reliable estimate of the efficacy of mepolizumab.

Table 4 Proportion of patients achieving a total daily prednisone dose of ≤10mg for a period of at least 8 consecutive weeks

Baseline Prednisone Dose Level Group	Placebo N=42	Mepolizumab 750mg N=43
All subjects (all prednisone doses)		
Number analyzed[1,2]	42	43
Responders[3], n (%)	18 (43)	36 (84)
Odds ratio vs. placebo	---	8.01
[95% CI]	---	[2.69, 23.78]
p-value	---	<0.001
<=30mg prednisone		
Number analyzed[1]	30	30
Responders[3], n (%)	17 (57)	26 (87)
Odds ratio vs. placebo	---	4.97
[95% CI]	---	[1.39, 17.82]
p-value	---	0.011
>30mg prednisone		
Number analyzed[1]	12	13
Responders[3], n (%)	1 (8)	10 (77)
Odds ratio vs. placebo	---	36.67
[95% CI]	---	[3.26, 412.26]
p-value	---	<0.001
Breslow Day Test[4] p-value	---	0.140

Data Source: Table 7.2

1. Cochran-Mantel-Haenszel analysis.
2. Adjusted for baseline prednisone (or equivalent) dose (<=30mg/>30mg).
3. Subjects who achieved a total daily prednisone dose of <=10mg for a period of at least 8 consecutive weeks.
4. Assesses homogeneity of the odds ratios across strata.

- The taper or weaning off prednisone can be considered beneficial as long as the disease remains well-controlled, based not only on blood eosinophil counts but also on an evaluation of the disease progression and the incidence, type, severity of the clinical flares occurring throughout the study. Such information is lacking although it is clear from the safety analyses that numerous HES-related events occurred during the study.

- Although agreed with the Regulatory Authorities, the primary endpoint, i.e. the proportion of patients achieving a daily prednisone dose ≤ 10 mg for at least 8 consecutive weeks, does not appear a hard endpoint, especially for subjects on 20 mg/day at baseline. This is illustrated by a response rate of 100% in the 14 placebo patients on baseline prednisone dose of 20 mg/day. Therefore, more weight is given to more stringent endpoints.

Treatment-by-region interaction

The Breslow-Day test shows statistically significant treatment by region interaction with a p-value=0.006. The treatment effect is evident in North America, with the response rates being 24% in placebo group and 86% in the mepolizumab group. On the other hand, no treatment effect can be seen in the Rest of the World region, with the response rates being 85% and 82% in placebo and active treatment groups, respectively (**Table 5**).

Table 5 Analysis of Proportion of Subjects who Achiewed a Total Daily Prednisone dose of <=10mg for a Period of at Least 8 Consecutive Weeks Stratified by Region (ITT population)

Baseline Prednisone Dose Level Group	Placebo N=42	Mepolizumab 750mg N=43
All subjects (both regions)		
Number analyzed[1,2]	42	43
Responders[3], n (%)	18 (43)	36 (84)
Odds ratio vs. placebo	---	5.34
[95% CI]	---	[1.98, 14.40]
p-value	---	<0.001
North America		
Number analyzed[1]	29	21
Responders[3], n (%)	7 (24)	18 (86)
Odds ratio vs. placebo	---	18.86
[95% CI]	---	[4.25, 83.59]
p-value	---	<0.001
Rest of the World		
Number analyzed[1]	13	22
Responders[3], n (%)	11 (85)	18 (82)
Odds ratio vs. placebo	---	0.82
[95% CI]	---	[0.13, 5.23]
p-value	---	0.834
Breslow Day Test[4] p-value	---	0.006

Data Source: Table 7.61

1. Cochran-Mantel-Haenszel analysis.
2. Adjusted for baseline prednisone (or equivalent) dose (<=30mg/>30mg).
3. Subjects who achieved a total daily prednisone dose of <=10mg for a period of at least 8 consecutive weeks.
4. Assesses homogeneity of the odds ratios across strata.

It can be seen in **Table 6** that the treatment wise proportions of baseline prednisone levels are different between the regions. This imbalance may, at least partially, explain the significant interaction, since, as noticed earlier the treatment effect seems to depend on the baseline prednisone level. Individual centers were not considered in the analyses because of the small number of subjects in each center.

However, since placebo patients in NA were likely to be more severe than those in the ROW, this could explain why they were more likely to drop out. Thus, the imbalance in severity across regions coupled with the imbalance in assignment to placebo, suggests that this interaction can be explained.

Table 6 Baseline Prednisone Dose (mg) by Region (ITT)

Baseline Prednisone Dose Level Group	North America		Rest of the World	
	Placebo N=29	Mepolizumab 750mg N=21	Placebo N=13	Mepolizumab 750mg N=22
All subjects (all doses), n	27[1]	21	13	22
Mean (SD)	32.1 (12.1)	27.1 (9.4)	26.5 (10.9)	31.3 (11.5)
<=30mg prednisone, n	17	16	11	14
Mean (SD)	24.1 (4.4)	22.7 (4.6)	22.3 (3.4)	23.8 (5.3)
>30mg prednisone, n	10	5	2	8
Mean (SD)	45.8 (7.6)	41.5 (4.9)	50.0 (0.0)	44.4 (6.2)

Data Source: Table 7.59 and Table 7.60

1. Baseline prednisone data missing for 2 subjects

Secondary endpoints.

In the pivotal study, secondary endpoints were met for steroid sparing effects and reduction of eosinophil counts. Skin manifestations and pruritus were not changed, Quality of life results did not show a clear effect. Comparisons of following secondary endpoints showed statistically significant overall difference between the response rates of mepolizumab and placebo groups:

1. proportion of subjects who maintained blood eosinophil count <600/ul for a period of at least 8 consecutive weeks during treatment period,
2. proportion of subjects who achieved a total daily prednisone dose of ≤7.5mg during the treatment period
3. proportion of subjects who were corticosteroid-free during the treatment period.

However, the Breslow-Day test revealed a statistically significant treatment by baseline prednisone dose level interaction (endpoints 1. and 2.; not statistically significant in endpoint 3 [P-value=0.075]). Further, it is well known that the power of Breslow-Day test to detect even rather large clinically meaningful differences between odds ratios across strata is rather poor. The reason for the observed interactions is that the response rates in the placebo group of ≤ 30 mg prednisone strata are constantly higher than in the placebo group of >30 mg prednisone, but the response rates in the mepolizumab group are very similar over baseline prednisone strata. The results give an evidence for the claim that the difference between mepolizumab and placebo treatments depends on the level of baseline prednisone dose. Overall odds ratio should not be used as a measure of efficacy of mepolizumab for those secondary endpoints while the Breslow-Day test revealed that the odds ratios are not similar across strata. If the Breslow-Day test is statistically significant for these secondary endpoints, it may not be appropriate to combine strata overall, and the results should be presented for each level of the stratification factor separately, which the applicant has done. It is clear that the odds ratios are much higher in those patients with higher baseline doses of prednisone and the applicant has failed to discuss the relevance of the results in those patients with lower baseline prednisone doses, and the implication this has on the appropriateness of treatment.

Post-hoc analyses
The overall exposure to prednisone as expressed by its average daily dose throughout the trial (secondary analysis) is an endpoint less likely to be biased. There was a substantial difference between the two treatment groups, especially in the group of patients with the higher baseline doses (see **Table 7**).

Table 7 Summary of the exposure to prednisone during the treatment period

	Placebo n=42	**Mepolizumab n=43**
All subjects	40	43
Baseline dose	30.3 (11.8)	29.2 (10.6)
Average daily dose	20.8 (11.9)	8.7 (6.8)
Days on prednisone	157 (81)	231 (58)
≤ 30 mg prednisone	28	30
Baseline dose	23.4 (4.1)	23.2 (4.9)
Average daily dose	16.0 (8.8)	8.0 (7.3)
Days on prednisone	177 (81)	225 (64)
> 30 mg prednisone	12	13
Baseline dose	46.5 (7.1)	43.3 (5.7)
Average daily dose	32.1 (10.6)	10.6 (5.1)
Days on prednisone	108 (60)	245 (41)

Although these were post-hoc analyses, the proportion of patients achieving a daily prednisone dose ≤ 10 mg for at least 24 consecutive weeks and the proportion of patients who became corticosteroid-free during the treatment and remained so until completion of the study are clinically very relevant endpoints. The differences were highly significant between treatment groups, and interestingly, these differences were very similar across the geographic regions for these more stringent endpoints. If the applicant can provide further convincing information regarding the nature of the withdrawals, these results could be seen as strongly supportive.

Control of end-organ damage
The pivotal trial does not provide any evidence of control of end-organ damage whereas it was emphasised by the CHMP that end-organ involvement should be the key secondary endpoint.

The long term clinical benefits for morbidity or mortality resulting from reduction of end-organ complications or costicosteroid sparing are not evident based of current studies. No improvement or deterioration was observed in Neurological Examinations, Pulmonary function tests, CT scans of the abdomen, sinuses, or chest at Week 36, Echocardiograms or skin (based on Skin photographs).

In spite of the protocol planning repeated skin and GI tissue biopsies in patients affected at baseline, data were only available for 3 patients, respectively. This might have permitted to collect useful supporting information on eosinophil infiltration in these tissues since the level of eosinophilia is not a true reflection of organ damage.

To explain the lack of any trends in end-organ improvement the applicant has argued that "this clinically stable patient population, a necessary part of the ethical basis of the study, may have resulted in quiescent disease such that the power of the study would be inadequate to detect any treatment differences in end-organ damage". However, examination of the numerous HES-related adverse events, some serious and even fatal, does not suggest such a quiescent disease. It is again emphasised that a proper analysis of HES-related adverse events should be conducted.

The wording of the indication in the SmPC should clearly state that no effect on organ damage has been demonstrated.

Study MHE100901: An Open-label Extension Study to Study MHE100185, to Evaluate Long-term Safety, Efficacy and Optimal Dosing Frequency of 750 mg Intravenous Mepolizumab in Subjects with Hypereosinophilic Syndrome (Interim Report)

This open-label study is an extension to Study MHE100185. It was designed to investigate the long-term safety, efficacy, and optimal dosing frequency of mepolizumab 750 mg IV infusion in subjects with various clinical manifestations of HES. The planned duration of the study was approximately 39 months. However, the individual subject's study participation could vary, depending on the time of entry and/or conclusion in Study MHE100185. This study is ongoing and an interim report was submitted (cut-off date: 03 September 2007).

The primary objective of this study was to evaluate the long-term safety of mepolizumab 750 mg IV infusion at maximum dosing frequency of once every month in subjects with HES.

Of the 85 subjects who participated in Study MHE100185, 78 subjects enrolled and received treatment in MHE100901 (ITT Population). As of the clinical cut-off date (3 September 2007), 61 subjects (78%) were continuing in the study, 17 subjects were withdrawn from the study (see Table 10).

A subject could be withdrawn from the study at any time at the investigator's discretion or at the request of the subject. The reason for withdrawal was documented for all subjects prematurely withdrawing from the study. The most common reasons for withdrawal were adverse events and lack of efficacy (6 subjects for each). All study subjects received mepolizumab 750mg IV in variable dosing schedules in 3 stages:
• **Stage 1**: HES Medication Taper and Stabilization Period
• **Stage 2:** Optimization of Dosing Frequency
• **Stage 3:** Assessment of Long-Term Safety and Efficacy

Table 10. Summary of patient disposition

Subject Disposition	Number (%) of Subjects Mepolizumab 750 mg		
	Previous Placebo N=38	Previous Mepolizumab N=40	Total N=78
Status			
Continuing as of clinical cut-off date	31 (82)	30 (75)	61 (78)
Withdrew from study	7 (18)	10 (25)	17 (22)
Reason for Withdrawal from Study			
Adverse event	3 (8)	3 (8)	6 (8)
Lack of efficacy	2 (5)	4 (10)	6 (8)
Consent withdrawn	1 (3)	2 (5)	3 (4)
Other	1 (3)	1 (3)	2 (3)

Results

Seven subjects (5 previous placebo subjects and 2 previous mepolizumab subjects) were erroneously enrolled in Stage 1 instead of Stage 2 as they were receiving daily prednisone dose of ≤10 mg. With the exception of Subject 153, all other subjects received from 3 to 6 mepolizumab infusions at a 4-week dosing interval during Stage 1 treatment. Subject 153 received 9 mepolizumab infusions with a variety of dosing intervals (ranging from 4 weeks to >24 weeks) during Stage 1 treatment. All 7 subjects progressed to Stage 2 from Stage 1.

Outcomes and estimation

A steroid sparing effect was observed in subjects who entered Study MHE100901 in Stage 2 with a daily prednisone (or equivalent) dose of ≤10 mg at the end of Study MHE100185. Almost all subjects (43/48, 90%) maintained at a daily prednisone (or equivalent) dose of ≤10 mg (as sole background therapy) for discrete periods of ≥12 weeks ("responders") over the time that they have participated in Study MHE100901. This steroid sparing effect was further demonstrated in post-hoc analyses that showed 30 of 43 responders maintained at a daily prednisone dose of ≤10 mg for discrete periods of ≥60 weeks during the study. More than half of the subjects (28/48, 58%) were prednisone free for discrete periods of at least 12 weeks during the time that they participated in the study. Among these 28 subjects, 19 remained prednisone free for discrete periods of ≥60 weeks.

Eighty-three percent of subjects (25/30) who entered Study MHE100901 at Stage 1 with a daily prednisone level >10mg had previously received placebo in Study MHE100185. A steroid sparing effect was observed in a total of 22 subjects (20 previous placebo subjects and 2 previous mepolizumab subjects) who achieved a daily prednisone (or equivalent) dose of ≤10 mg (as sole background therapy) for discrete periods of ≥12 weeks ("responders") during the time that they participated in Study MHE100901. The data from post-hoc analyses showed that 15 of the previous placebo subjects (15/25, 60%) remained at their prednisone daily dose of ≤10 mg for discrete periods of ≥60 weeks and 8 of these 15 subjects were able to discontinue prednisone dosing. For the subjects who previously received placebo in Study MHE100185, 50% of subjects (12/24) achieved a daily prednisone dose of ≤10 mg at Week 5 and 83% of these subjects (19/23) achieved daily prednisone dose of ≤10 mg at Week 12.

The data shows that patients previously treated with placebo that did not reach corticosteroid sparing effect with placebo in study MHE100185, could respond to mebolizumab in this study. 60% of the subjects with previous mepolizumab had dosing interval over 10 weeks when guided by HES clinical signs and symptoms and eosinophil count. This suggests that the proposed posology needs further justification. No statistical calculations have been made.

Eosinophil counts were initially higher in previous placebo-treated patients but were lower during mepolizumab in this study. No statistical calculations have been presented. pVAS and erythema/edema scores did not give any further information on efficacy of mepolizumab in controlling HES symptoms. This study in mainly a descriptive study.

Supportive studies

Compassionate use program

Report ZM2006/00080/00: Treatment with Mepolizumab in a Global Compassionate Use Program – Interim Report

This is an interim report covering the mepolizumab compassionate use experience from April 2001 to 16 July 2007, with SAE reports through 30 April 2008: Initial Compassionate Use (Initial CU) Program, MHE104317, Named Patient Supply (NPS) Program

Study Participants

Initial CU Program: 7 centers: NPS Program: 17 centers: All patients in the Initial CU Program, MHE104317 study and the NPS Program received open-label mepolizumab treatment. In the Initial CU Program, doses ranged from a single IV infusion of 50mg to 1300mg IV at various frequencies for up to one year. In the MHE104317 study and NPS Program, mepolizumab was administered by IV infusion up to 750mg (10 mg/kg if body weight was <45 kg) at dosing intervals that were optimized for each patient depending on the individual's blood eosinophil count and clinical presentation but not more frequently than every 4 weeks. Physicians were informed that GSK had no clinical experience of treating HES patients with mepolizumab at doses greater than 750mg every 4 weeks.

Outcomes/endpoints
Since the Initial CU Program was initiated on investigator request basis, there were no specific efficacy endpoints defined. Efficacy and safety information available in this report were communicated by physicians to GSK.

Outcomes and estimation
Initial CU Program
Eleven out of 14 patients who had HES reported clinical benefit as a result of receiving mepolizumab. The following improvements were reported: elimination of at least one symptom (7 patients); non-specific improvement (2 patients); stable condition (1 patient), and maintenance of clinical benefit longer than 14 months (1 patient - Canada 1C) until suffering from bronchitis. Of the remaining 3 patients, 2 (France 1C and USA 1C) had transient effects (couple of days) of clinical benefit. No benefit was reported for Netherlands 1C, the 3-month-old infant. No worsening of symptoms was reported in correspondence from the treating physicians. All 14 patients with HES reported having tried prednisone with little or no success prior to starting treatment with mepolizumab. The dose of prednisone that was being prescribed when mepolizumab was started for ten patients ranged from 10 to 60mg/day (50% 20mg or less and 50% 35mg or above). Ten of 14 patients (71%) specifically stated that they were able to reduce their dose to 10mg. Four of these 10 patients were able to reduce their steroid dose to 5mg/day and 5 patients reported eliminating steroids from their dosing regimen. Twelve patients had a reduction in eosinophil count after receiving mepolizumab treatment. Two patients (France 1C and USA 1C) had a reduction in eosinophil count although the effect lasted only for a short period (couple of days). Doses of mepolizumab ranged from 5 to 10mg/kg and 500mg to 1300mg in the Initial CU Program with the predominate dose for 10/15 patients being 750mg. Six patients received infusions at 2 months or greater intervals and six received infusions every 14 days to 1 month.

Study MHE104317 AND NPS databased patients

Twenty-one patients had a variety of tests performed and the majority of them had a stable status at each timepoint. Too few patients were assessed for each test at each timepoint to provide meaningful results. Out of 40 patients, eosinophil data were only available for 18 patients. A reduction in median eosinophil

count was observed within 4 weeks of the first infusion and was generally maintained over time. Twenty six patients had assessments of flare of their HES. Overall, the majority of patients had no flare of HES over the past 3 months reported between Weeks 12 and 60. For the few patients who experienced a flare of HES, the flare occurred only once in the past 3 months and was of mild or moderate intensity. Although the number of patients was small, no flares were observed during Weeks 60 through 84. Overall, 85% of patients (28/33) took at least one concomitant HES medication to treat their disease: the majority of patients took corticosteroids. Fifty-five percent of patients (18/33) took prednisone, 9% (3/33) hydroxycarbamide, 6% (2/33) interferon, and 3% (1/33) imatinib mesylate. Five patients were followed up to assess rebound of HES symptoms after cessation of mepolizumab treatment. All five patients had a Safety Follow-up Visit three months after the discontinuation of mepolizumab. Rebound of HES symptoms was reported in one patient of the five patients.

NPS/Non-databased Patients
Of the 14 patients for whom some level of benefit was reported, complete control of disease was reported for nine and control/resolution of some symptoms was reported for three. Of these latter three patients, periods of control and resolution of some flares were reported for one patient (England 1N). No worsening or improvement of disease was reported for France 9N; and Patient Belgium 2N is believed to be continuing with mepolizumab infusions but no results have been reported. A reduction in eosinophil counts was reported by physicians for 11 of the 20 patients (55%) although absolute eosinophil counts for only 4 patients were available in the documentation. A reduction in steroids or achievement of steroid sparing was reported for 10 of the 20 patients (50%). All patients received doses of 750mg and the majority (75%, 11/16 patients) received drug initially once monthly. Dose frequency later in the program varied from 4 weeks to 17 weeks with a mean frequency (for the 16 patients where dosing frequency is known) of 10.3 weeks. A reduction in steroids or achievement of steroid sparing was reported for 10 of the 20 patients (50%). Three of the 20 patients entered the study not taking steroids; however one subsequently received steroid to treat their disease and has not reduced the steroid to zero. Of the remaining 7 patients, it is known that 6 entered the study taking steroids but whether they have been able to reduce the dose as yet is unknown. A reduction in eosinophil counts was reported by physicians for 11 of the 20 patients (55%) although absolute eosinophil counts for only 4 patients were available in the documentation.

The compassionate use program gives only some additional information on steroid sparing effect of mepolizumab in HES patients.

Target population
The pivotal trial could only support a restricted indication in terms of target population, which corresponds to 'HES well controlled with corticosteroid therapy'. No recommendations can be inferred for patients with acute presentations, for patients who have not yet received corticosteroid therapy or for patients unresponsive to corticosteroid therapy. Allegedly, patients from the compassionate use programme were more severe but the sparse data provided are not sufficient to support any broader claim.

Clinical safety

Since mepolizumab is a monoclonal antibody interfering with immunological pathways, the immunological safety i.e. infections and malignancies are of concern. Also, development of anti-mepolizumab antibodies and rebound effects should be watched for. No preclinical or clinical safety data are available of other anti-IL-5 antibodies for comparison. Only limited number of animals (3 cynomolgus monkeys) have been studied during long-tem use of mepolizumab (6 months).

Limited data on safety of mepolizumab compared to placebo is available in relation to proposed target population; only 42 patients have been compared to placebo with proposed posology and indication. Long-term data with the proposed posology is missing. In the compassionate use program 13 patients have been given mepolizumab for 12 months or more.

Patient exposure
Given the rarity of the disease, the overall size of the short-term safety database (around 500 subjects) treated with 1-4 infusions is acceptable although it does not allow for identification of rare events. However, the size of the long-term safety database is limited to the population of the extension trial in HES and the compassionate use program with exposure up to 3 years, and anecdotally 7 years. This represents about 150 patients and would need to be extended post-marketing in the frame of a patient registry such as proposed by the applicant in their RMP.

The total exposure to mepolizumab in the pivotal trial and its open label extension is shown in **Table 11** and **Figure 4**. Overall, the number of infusions in the 81 patients exposed ranged from 1 to 34 (median = 14); most patients (60/81; 74%) received at least 11 infusions of mepolizumab.

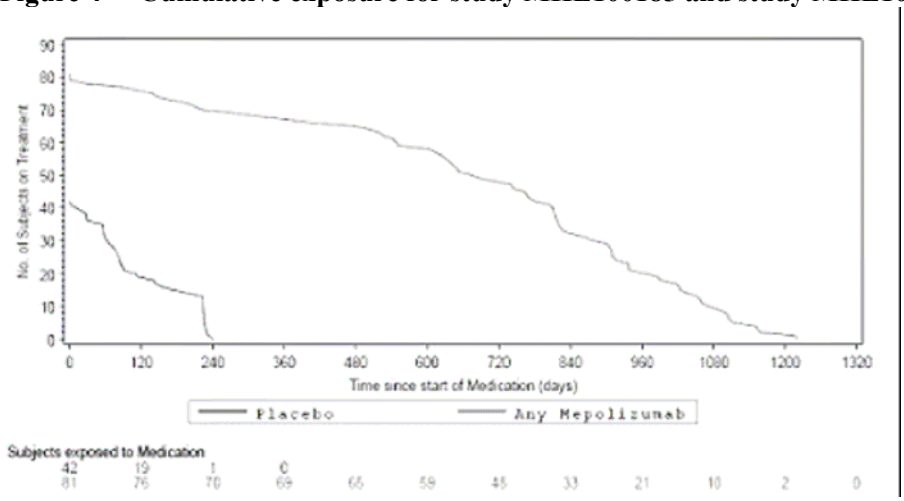
Table 11 Total exposure in HES clinical trials MHE100185 and MHE100901

Study	Treatment	Number of Subjects	Median Duration-Months (Min-Max)	Total Exposure in Subject Years
MHE100185	Placebo	42	3.3 (<1-8)	15
	Mepolizumab	43	7.4 (1-9)	24[a]
MHE100901	Mepolizumab	78	22.3 (<1-35)	134[b]
MHE100185 + MHE100901	Mepolizumab	81	27 (<1-40)	161[c]

Data Source: CSR MHE100185 Table 8.1, CSR MHE100901 Table 7.2 and m5 MHE-ISS Table 4.2

a. Exposure for MHE100185 was calculated from first to last MHE100185 infusions.
b. Exposure for MHE100901 was calculated from first to last MHE100901 infusions.
c. Exposure for "MHE100185+MHE100901" was calculated from first MHE100185 infusion to last MHE100901 infusion. Because for some subjects there was a gap between the last MHE100185 infusion and first MHE100901 infusion, the total exposure is therefore greater than the sum in exposure for the individual studies.

Figure 4 Cumulative exposure for study MHE100185 and study MHE100901 combined



Common adverse events:
Most AEs in the pivotal HES-study were not considered drug-related. The adjustment for duration of exposure indicated that the frequency of some side effects was higher among mepolizumab-treated patients than among subjects treated with placebo. These higher incidences were reported for upper respiratory tract infections, myalgia, rhinitis, bronchitis, and urticaria. However, statistical comparisons have not been presented in the study report after these adjustments. In the pivotal study, the adverse effects were more common on the day of infusion in the mepolizumab group compared to placebo group,

especially skin and general symptoms as well as pain (myalgia and arthralgia). The applicant has clarified how the side effect were distributed between NA and RoW.The cumulative incidence of any adverse event during treatment by first occurrence was very high with mepolizumab (100%) and placebo (98%) in clinical studies with HES patients.

Pharyngitis (13%), URTI (18%) and headache (37%) were very common side effects in healthy volunteers, who received mepolizumab. No significant AE findings compared to placebo were reported in multiple dose asthma studies from IV mepolizumab. However, in study SB-240563/006, an increasing number of subjects with borderline QT prolongation are observed along time in all three treatment groups, including placebo (the IV treatment was given at baseline, at week 4 and at week 8). The effect is somewhat dose-dependent. Rhinitis and eczema were more common with mepolizumab than with placebo in single dose asthma studies. In patients with atopic dermatitis, fatigue and oedema were considered mepolizumab-related. No mepolizumab-related common AEs have been described in the dossier in studies with adult or paediatric patient with EE.

Severe adverse events
The majority of SAEs reported were considered related to the patient's underlying disease (HES) or medical history. They should be analysed in the context of the disease control.

In longer duration of treatment of HES patients, significant proportion of subjects (37%) had serious adverse events. None of the SAEs reported in study MHE100185 (12 subjects = 14%) were considered related to investigational treatment. In study MHE100901, one subject had non-fatal SAEs that were considered to be possibly related to investigational treatment (optic neuritis, transverse myelitis, and spinal disorder). In the compassionate use program, one patient suffered from lobar pneumonia, one from polyarthritis and fever, one abnormal sputum and bronchitis and one hepatic vein thrombosis, which were considered mepolizumab-related.

In the study of patients with atopic dermatitis, one subject (601 in the SB-240563 group) suffered from a drug-related severe side-effect (severe dermatitis). In paediatric EE, none of the SAEs reported in two subjects (chest discomfort, asthma, sinusitis, eosinophilic oesophagitis, oesophageal injury, foreign body trauma) were considered to be drug-related. In investigator-sponsored studies, two subjects have experienced non-fatal SAEs (retinal detachment in Subject AI-012 and cough, dyspnoea, lymphadenopathy, malaise, pyrexia, and wheezing in Subject AI-031), which were not considered related to the investigational product.

Deaths
In the pivotal study, one death was reported (cardiac arrest), the subject received mepolizumab but the death was not considered drug-related. All deaths during longer treatments (Study MHE100901) were in previous mepolizumab group. Over the duration of the controlled trial and its open label extension, 4 deaths (5%) occurred in the 81 patients exposed to mepolizumab; they all occurred amongst patients initially treated with mepolizumab (after approximately 4 – 22 months). Mortality in this population allegedly with stable corticosteroid controlled and “quiescent” disease raises some concern. Two of the deceased patients experienced worsening of their cardiac condition; cardiac events (serious or not) should be further described and discussed.

11 (7%) out of 156 subjects participating in HES clinical trials and compassionate use program have died as of the SAE by 30 April 2008. Two deaths (one due to angioimmunoblastic T-cell lymphoma and the other due to multi-organ failure/progression of HES) were considered possibly related to mepolizumab treatment (1.3% of all HES clinical trial patients) by the investigator. One additional death (progression of carcinoma) in the Compassionate Use Program was reported in June 2008 after the SAE cut-off date (30 April 2008), further information of this patient has not been reported. There has been one death reported in studies in other indications than HES in a study with a total of 20 subjects with eosinophilic bronchitis

(with or without asthma). The patient was treated with mepolizumab and the patient died about 9 month after the last infusion, the reason for death is unknown.

Mortality in the whole HES population (study and compassionate use) has been represented with Kaplan-Meier curve but has not been further discussed by the applicant with reference to historical data.

Laboratory findings and exploratory markers
In HES-studies, low haemoglobin and red blood cell count appeared more often in mepolizumab-treated patients than placebo-treated patients. The frequency of low lymphocytes also increased along with mepolizumab-treatment. Alkaline phosphatase showed mean increase in subjects in the mepolizumab group, but abnormal mean values were not recorded. Abnormal CPK, GGT and total bilirubin values were only observed in the mepolizumab groups group. In any case, the increase in these parameters should be mentioned in the SmPC.

No significant increasing in abnormal ECG-findings were observed in the pivotal and the following extension study. The applicant should present the proportion of subjects having borderline QT and QTc prolongations in each treatment arm along time in the pivotal study and also in the open label extension study MHE100901.

High IL-5 levels could be detected in mepolizumab group in most of patients from the week 12 onward during the treatment period. The result may indicate that the high IL-5 concentration is not a result of drug interference with the analysis method, but rather a treatment effect. However, the eosinophil counts were not higher in the mepolizumab group.

Withdrawals because of adverse events
Five subjects were withdrawn in Study MHE100185 (4 placebo group, 1 mepolizumab group) five in Study MHE100901, and two in the Compassionate Use Program (overall 12 patients). None of the AEs leading to withdrawal in Study MHE100185 or the Compassionate Use Program were considered related to treatment by the investigator. In Study MHE100901, three of the five withdrawals were considered related to treatment by the investigator and included optic neuritis and transverse myelitis (reported as nonfatal SAEs), angioimmunoblastic T-cell lymphoma (fatal), and urticaria (potential infusion reaction was reported by the investigator on follow-up). The infusion reaction was considered to be related to mepolizumab and led to withdrawal. In non-HES studies, adverse events leading to withdrawal have been related to exacerbation of the underlying disease; asthma (4 in multiple dose asthma studies; 1 in placebo and 3 in mepolizumab group); eosinophilic oesophagitis (1 in placebo group).

AEs of special interest
- Based on current data, the risk of hypersensitivity and infusion reactions appears to be low, with only a few reports (1 hypersensitivity, 2 infusion reactions), all of which were non-serious and mild-to-moderate in severity.
- With regard to a theoretical increased risk of infections, respiratory tract infections (URTI, bronchitis, and rhinitis) were reported more frequently on mepolizumab than on placebo and this in spite of lower corticosteroid doses. These infections are listed as ADRs in the SmPC. However, the applicant should provide a more detailed analysis of all SAEs of pneumonia.
- Malignancies are another theoretical concern with immunomodulatory biologics; however, the probability of reduced host surveillance for neoplasia subsequent to treatment with an anti-IL-5 mAb is likely to be low due to the targeted mechanism of action. Complicating this assessment is the natural history of HES itself and the use of immunosuppressive agents to treat the disease. Indeed, there were 3 cases of non-Hodgkin lymphomas (NHL) in 81 patients exposed in the pivotal trial and its extension. One patient developed angioimmunoblastic T-cell lymphoma with dysproteinemia (AILD), which the investigator considered possibly related to mepolizumab, but unlikely considering the natural history of the disease. Two other reports consisted of one mycosis fungoides and one

lymphomatoid papulosis, both of which were assessed as unrelated to mepolizumab. The increased risk of NHL in the context of the disease should be addressed in the SmPC.

- A full QTc assessment for the mepolizumab development programme has been provided by the applicant. QTc prolongation does not appear to be a concern with mepolizumab based on data currently available.

Immunogenicity

The applicant should develop more robust assays for detecting anti-mepolizumab antibodies in patient samples, especially the issue of interference with IL-5 and free mepolizumab.

- Based on the data presented, mepolizumab seems to be associated with a low incidence of immunogenicity (2% overall; 9% (4/43) in the pivotal trial over 9 months) but this may be underestimated due to the limitations of the current bridging assay. Furthermore, the detection of neutralising antibodies is unreliable. Even if the immunogenicity rate seems low, the potential of mepolizumab to induce antibodies is of concern since a lack of interference with the activity of mepolizumab cannot be ruled out in the 2 patients with high titres.

- No data on long-term immunogenicity are currently available. The applicant should analyse and report all samples collected for immunogenicity testing (studies SB-24053/036 and MHE100901 are of special interest). Should a marketing authorisation be granted, the submission of long-term immunogenicity from ongoing and future trials should be the purpose of a post-marketing specific obligation.

- Finally, immunogenicity has been addressed in the SmPC.

Withdrawal effects

There are limited data available to evaluate whether observations of "rebound" are related to HES exacerbation/disease progression or specifically related to an effect of mepolizumab mediated through IL-5. The potential for disease exacerbation upon withdrawal of mepolizumab has been adequately addressed in the SmPC and in the RMP.

Pharmacovigilance system

The CHMP considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management plan

3.5. Overview of Study Protocols for the Pharmacovigilance Plan

Study	Protocol Status	Protocol Version	Planned submission date of interim data	Planned date for submission of final data
MHE100901, Open-label long-term safety study in patients with HES	Ongoing	06Mar2006	Interim report to be submitted with MAA Sep'08	Final report available when mepolizumab is commercially available 2010 (EU only)
MHE104317/Named Patient Supply	Ongoing	06Aug2007	Interim report to be submitted with MAA Sep'08	Final report available when mepolizumab is commercially available 2010 (EU only)
Observational Cohort Study/Registry	Not applicable	Planned	Annual summary will be included as appendix to PSUR	Final report when all patients complete 5 years of monitoring 2017/2018
Prospective clinical study in paediatric patients with HES	Not applicable	Planned	Not applicable	2015

Executive summary of the Observational Cohort Study/Registry

HES is an extremely rare condition. Prevalence is estimated to be in the range of 1- 2/100,000. Published data are fragmented, consisting largely of limited case series and individual reports. Recently, there have been major advances in understanding clinical sub-types of HES and in development of new treatments. The overall goal of this study is to obtain further information on the adverse event profile of both mepolizumab, a new therapy for HES, and existing HES treatments in a clinical practice setting. Furthermore, information will be gathered on the clinical course of treated HES over time to see if any correlations exist between clinical outcomes and treatments. It is proposed to recruit a cohort of 700 patients with a diagnosis of HES by standard criteria and with a negative test for the FIP1L1-PDGFRA fusion gene (FIP1 gene), or if not tested or unknown, patients without myeloproliferative clinical features. Eligible patients must be receiving treatment with either mepolizumab or other drug therapies for HES. Participation by physicians and patients is voluntary.

Specific objectives

Safety

a) To estimate rates of specific adverse events in patients undergoing treatment with either mepolizumab or other drug therapies for HES. Adverse events of interest will include but will not be limited to those identified as either identified or potential risks in the Risk Management Plan (RMP).

b) To determine risk factors, if any, for adverse events in HES patients undergoing treatment with mepolizumab or other drug therapies for HES, including demographic characteristics, co-morbidities, drug therapies and history of the disease itself.

Disease Outcomes

a) To determine HES clinical status over time including end organ involvement and disease flares;

b) To assess the effect of mepolizumab and other therapies on the above clinical outcomes and thus the clinical history of treated HES over time.

The study will recruit an equal number of Mepolizumab-treated patients, and patients treated with other drug therapies; patients will be monitored for a period of five years.

The study will be guided by a Steering Committee comprising clinical experts in the treatment of HES and GSK staff and will be operationalised by an independent external group experienced in conducting registry activities.

As the applicant also pointed out, a major challenge from the statistical point of view is the potential for confounding in an observational cohort. Namely the subjects treated with mepolizumab and those not treated with mepolizumab may differ from each other in observed and unobserved characteristics at the time of entering into the cohort. These characteristics may not only predict the future outcomes but also the future treatment decisions which cause time-dependent confounding. The applicant hints using the propensity score approach for adjusting for such confounding but the general statistical approach does not specify any further details how such an adjustment is made. The protocol with adequate details has been provided for review and has been accepted.

Summary of the risk minimisation plan

At this stage no additional risks were identified for inclusion to the RMP. As the SmPC is the main risk minimisation tool, several comments arising during the RMP assessment relate to the SmPC. A more detailed protocol for the paediatric study in HES is not currently available. This protocol is being developed for submission to the PDCO as part of the mepolizumab PIP later in 2009. The RMP will be updated to include further information on this protocol once the detailed protocol for the study has been agreed with PDCO.

Safety concern	Routine risk minimisation activities sufficient?	If yes, provide a description of routine activity and justification
Important identified risks		
Immunogenicity	Yes	Routine activity includes appropriate labelling. Warnings and precautions, Section 4.4 of the SmPC, includes information on findings, clinical outcomes and assays. Information on findings and clinical outcomes are repeated in Section 4.8 of the SmPC. Risk communication in the product labelling is considered to be the primary risk minimization

Safety concern	Routine risk minimisation activities sufficient?	If yes, provide a description of routine activity and justification
		tool and sufficient to inform prescribers.
Important identified risks		
Hypersensitivity, including infusion reactions	Yes	Routine activity includes appropriate labelling. Warnings and precautions, Section 4.4 of the SmPC, includes information on signs and symptoms of reactions, frequency and outcomes. Information on signs and symptoms and frequency are repeated in Section 4.8 of the SmPC. Risk communication in the product labelling is considered to be the primary risk minimization tool and sufficient to inform prescribers.
Important potential risks		
Rebound of HES symptoms	Yes	Routine activity includes appropriate labelling. Warnings and precautions, Section 4.4 of the SmPC, includes appropriate guidance on monitoring for disease exacerbation when discontinuing treatment with BOSATRIA. Additionally, Section 4.2 advises that BOSATRIA should be initiated by or in consultation with a physician experienced in the management of HES. Risk communication in the product labelling is considered to be the primary risk minimization tool and sufficient to inform prescribers.

Safety concern	Routine risk minimisation activities sufficient?	If yes, provide a description of routine activity and justification
Important potential risks		
Alterations in immune response, including infections and malignancies	Yes	Routine activity includes appropriate labelling for the postential risks of both infections and malignancies. Infections: Warnings and precautions, Section 4.4 of the SmPC, includes a precautionary statement regarding the risk of infections during treatment with mepolizumab, but also emphasizes ruling out parasitic infections as the cause of hypereosinophilia prior to initiating treatment with BOSATRIA. Additionally, information on specific adverse reactions reported and the frequency are included in Section 4.8 of the SmPC. Malignancies: Warnings and precautions, Section 4.4 of the SmPC, includes a precautionary statement regarding the known risk of lymphoma in patients with lymphoproliferative HES and a statement regarding the potential for unmasking a pre-existing malignancy subsequent to steroid reduction. Risk communication in the product labelling is considered to be the primary risk minimization tool and sufficient to inform prescribers.

Safety concern	Routine risk minimisation activities sufficient?	If yes, provide a description of routine activity and justification
Important missing information		
Children (<18 years)	Yes	Routine activity includes appropriate labelling. Posology, Section 4.2 of the SmPC, includes a statement that BOSATRIA is not recommended for use in children below age 18 due to insufficient data on safety and efficacy. Also Therapeutic indications, Section 4.1, specifies use in adults only. Risk communication in the product labelling is considered to be the primary risk minimization tool and sufficient to inform prescribers.
Elderly patients	Yes	Routine activity includes appropriate labelling. Posology, Section 4.2 of the SmPC, includes a statement that there are limited data available on the use of BOSATRIA in patients aged 65 years and over, but there is no evidence that a different dose is required. Information on elderly is also included under special populations in Section 5.2 of the SmPC. Risk communication in the product labelling is considered to be the primary risk minimization tool and sufficient to inform prescribers.

Safety concern	Routine risk minimisation activities sufficient?	If yes, provide a description of routine activity and justification
Important missing information		
Pregnant or lactating females	Yes	Routine activity includes appropriate labelling. Pregnancy and lactation, Section 4.6 of the SmPC, includes statements that there are no adequate data on the use of BOSATRIA in pregnant women and the effect on human pregnancy are unknown. Additionally, there are statements there are no data on the excretion of BOSATRIA in human milk and safe use in humans during lactation has not been established. Pre-clinical findings on both pregnancy and lactation are included in sections 4.6 and 5.3 of the SmPC. Risk communication in the product labelling is considered to be the primary risk minimization tool and sufficient to inform prescribers.
Patients with renal or hepatic impairment	Yes	Routine activity includes appropriate labelling on both renal and hepatic impairment. Renal impairment: Posology, Section 4.2, and special populations described in Section 5.2 of the SmPC, includes statements that no specific studies in patients with renal impairment have been conducted and that that there are limited data on the use of mepolizumab in patients with creatinine clearance values between 50-80 ml/min. There is no evidence that these patients require a different dose than patients with creatinine clearance values ≥80 ml/min; there are no data available in patients with creatinine clearance values <50 ml/min.

Safety concern	Routine risk minimisation activities sufficient?	If yes, provide a description of routine activity and justification
Important missing information		
		Hepatic impairment: Posology, Section 4.2, and special populations described in Section 5.2 of the SmPC, includes statements that studies in patients with hepatic impairment have not been conducted. Risk communication in the product labelling is considered to be the primary risk minimization tool and sufficient to inform prescribers.
Sub-populations with other classifications of HES (or relevant genetic mutation)	Yes	Routine activity includes appropriate labelling. Therapeutic indications, Section 4.1 of the SmPC, include a statement that BOSATRIA is indicated for patients with HES who lack the FIP1L1-PDGFR fusion gene. Additionally, Section 4.2 advises that BOSATRIA should be initiated by or in consultation with a physician experienced in the management of HES. Warnings and precautions, Section 4.4 of the SmPC, includes a statement that the risk-benefit profile of BOSATRIA has not been established in patients with the FIP1L1-PDGFR fusion gene. Risk communication in the product labelling is considered to be the primary risk minimization tool and sufficient to inform prescribers.

Safety concern	Routine risk minimisation activities sufficient?	If yes, provide a description of routine activity and justification
Important missing information		
Subpopulations with other eosinophilic driven diseases	Yes	Routine activity includes appropriate labelling. Therapeutic indications, Section 4.1 of the SmPC, include a statement that BOSATRIA is indicated for patients with HES who lack the FIP1L1-PDGFR fusion gene. Additionally, warnings and precautions, Section 4.4 of the SmPC, includes a statement that the risk-benefit profile of BOSATRIA has not been established in patients with non-HES eosinophilic disease. Risk communication in the product labelling is considered to be the primary risk minimization tool and sufficient to inform prescribers
Patients with lymphoma, haematological malignancy, and advanced and/or metastatic solid tumors	Yes	Routine activity includes appropriate labelling. Therapeutic indications, Section 4.1 of the SmPC, include a statement that BOSATRIA is indicated for patients with HES who lack the FIP1L1-PDGFR fusion gene. Additionally, warnings and precautions, Section 4.4 of the SmPC, includes a statement that secondary causes of hypereosinophilia must be ruled out before initiating therapy with BOSATRIA. Additionally, this Section includes a statement that the risk-benefit profile of BOSATRIA has not been established in patients with secondary causes of hypereosinophilia. Risk communication in the product labelling is considered to be the primary risk minimization tool and sufficient to inform prescribers.

Safety concern	Routine risk minimisation activities sufficient?	If yes, provide a description of routine activity and justification
Limited experience in the following groups:		
Patients with severe refractory HES or newly diagnosed HES	Yes	Routine activity includes appropriate labelling. Therapeutic indications, Section 4.1 of the SmPC, include a statement that BOSATRIA is indicated for patients with HES who are on stable doses of steroids and who lack the FIP1L1-PDGFR fusion gene. Additionally, Section 4.2 advises that BOSATRIA should be initiated by or in consultation with a physician experienced in the management of HES. Risk communication in the product labelling is considered to be the primary risk minimization tool and sufficient to inform prescribers.
Patients taking doses outside the proposed regimen	Yes	Routine activity includes appropriate labelling. Posology, Section 4.2 of the SmPC, includes a statement that the standard dose is 750 mg (3 x 250 mg vials) every 4 weeks. Additionally, Section 4.9 of the SmPC states that single intravenous doses of up to 1500 mg have been administered to 5 adult patients with eosinophilic esophagitis without evidence of dose-related toxicities. Risk communication in the product labelling is considered to be the primary risk minimization tool and sufficient to inform prescribers.
Patients of different racial and/or ethnic origin	Not applicable	None proposed

III. ORPHAN MEDICINAL PRODUCTS

Mepolizumab is a fully humanised monoclonal antibody (IgG1, kappa, mAb) which is specific for human interleukin-5 (IL-5). Mepolizumab is being developed for the treatment of hypereosinophilic syndrome (HES). One textbook cites incidence of 0.1/100,000 for all HES [Wardlaw, 2006]. Orphan status was granted on July 29, 2004; the number in the Community Register of Orphan Medicinal Products is EU/3/04/213. According to the conclusion of the COMP (Opinion dated 29/07/2004) the condition hypereosinophilic syndrome affects about 7,000 individuals in the EU.

To date, one other product, Glivec (imatinib), has received orphan medicinal product designation for a HES-related indication in the European Community (EU). Glivec was approved in October 2006 for the orphan indication 'treatment of adult patients with advanced HES and/or CEL with FIP1L1-PDGFRA gene'.

The orphan drug designation of mepolizumab did not base on the criterion of "significant benefit". Glivec has received orphan drug designation in the treatment of HES with FIP1L1-PDGFRA gene and the proposed indication for mepolizumab is HES without the FIP1L1-PDGFR fusion gene.

IV. BENEFIT RISK ASSESSMENT

IV.1 Clinical context

HES is managed initially with moderate-to-high dose corticosteroids to rapidly reduce blood eosinophils. Although not formally approved for HES, corticosteroid therapy has been used for decades in clinical practice as first line treatment for FIP1 negative HES both in the EU and elsewhere. Many patients respond to treatment with corticosteroids. However, toxicity with long-term use and/or lack of efficacy lead to a variety of cytotoxic and immunomodulatory agents including hydoxyurea, vincristine, methotrexate, interferon alpha, immunoglobulin, and cyclosporine being used as second line agents. Therefore, steroid sparing could be considered as a clinically important benefit in the long-term management of symptoms and/or prognosis of the condition.

IV.2 Benefits

Claimed benefits come from the single pivotal study:
Primary endpoint: Prednisone ≤ 10mg/day for 8 Consecutive Weeks
Responders: Placebo 18/42 (**43%**) vs. Mepolizumab 750mg 36/43 (**84%**); p < 0.001
Secondary endpoints:
1. Proportion of subjects who maintained a blood eosinophil count of <600/µl for a period of 8 consecutive weeks during the Treatment Period.
Responders: Placebo 19/42 (**45%**) vs. Mepolizumab 750mg 41/43 (**95%**); p < 0.001
2. Time until treatment failure with treatment failure defined as clinical worsening requiring other HES based therapy or an increase of prednisone dose to >60mg/day per discretion of the investigator, or withdrawal from the study for any reason.
Treatment failure (withdrawal): Placebo 29/42 (**69%**) vs. Mepolizumab 750mg 9/43 (**21%**); p < 0.001
3. Proportion of subjects who achieved a total daily prednisone dose of ≤7.5mg (sub-adrenal threshold) during the Treatment Period.
Responders: Placebo 21/42 (**50%**) vs. Mepolizumab 750mg 37/43 (**86%**); p < 0.001
4. Proportion of subjects who were corticosteroid-free (for at least one day) during the Treatment Period.
Responders: Placebo 10/42 (**24%**) vs. Mepolizumab 750mg 34/43 (**79%**); p < 0.001

5. Mean total daily dose of prednisone.
Adjusted mean dose at week 36 (LOCF):
Placebo **21.8 mg** (SE 1.9) vs. Mepolizumab 750mg **6.2 mg** (SE 1.9); $p < 0.001$
6. Proportion of subjects who achieved total prednisone daily doses 12 weeks after randomization in the following categories:

0mg,	Responders: Placebo 5/42 (**14%**) vs. Mepolizumab 750mg 18/43 (**44%**)
2.5-7.5mg,	Responders: Placebo 51/42 (**14%**) vs. Mepolizumab 750mg 15/43 (**37%**)
10mg	Responders: Placebo 4/42 (**11%**) vs. Mepolizumab 750mg 2/43 (**5%**)
>10mg:	Responders: Placebo 21/42 (**60%**) vs. Mepolizumab 750mg 6/43 (**15%**)

$p < 0.001$

Robustness of results:
-The statistically significant difference in the Primary Endpoint in favour of mepolizumab was only observed in NA population and not in the RoW population. Furthermore, the result has the potential to be biased, since the withdrawals may have been guided based on eosinophil counts, which were different between mepolizumab and placebo groups. Therefore, it can be assumed that the effect on eosinophil count guided the decisions of investigators to withdraw the patient. The pivotal information about the exact reasons for withdrawal is missing since it has not been documented and reported to be able to estimate the reliability of this primary efficacy result of mepolizumab. In addition, the placebo group included a substantial number of patients that were not well controlled at baseline. Therefore, the number of responders in the Best Case analysis should be much higher in the placebo group, which would result in non significant results.
-There is some evidence that baseline prednisone dose and the severity of disease could have determined the response rate to placebo in the two regions, since 37% of the placebo patients belonged to the >30mg baseline prednisone group in NA and only 15% in RoW belonged to this group. The lower effect of placebo on more severe disease leading to withdrawal may explain the treatment-by-region interaction.

Clinical relevance of the results
-HES is a severe disease having significant mortality because of end-organ damage. The studies performed with mepolizumab do not address the end-organ damage or disease control based on symptom frequency or mortality. Therefore, it is not known if the patients will eventually benefit from Bosatria treatment in terms of decreased disease activity, treatment adverse events form other drugs or mortality.

Dosage justification
It is unclear, what are the justifications of the suggested dosage, since disease control has not been fully evaluated or reported when mepolizumab has been given to HES patients.

IV.3 Risks

- Quality of the product: The validation of mepolizumab drug substance manufacturing process is incomplete and comparability between the pilot and commercial scale drug substance has not been sufficiently demonstrated.
- Common adverse events: The adjustment for duration of exposure indicated that the frequency of some side effects was higher among mepolizumab-treated patients than among subjects treated with placebo. These higher incidences were reported for upper respiratory tract infections, myalgia, rhinitis, bronchitis, and urticaria. In the pivotal study, the adverse effects were more common on the day of infusion in the mepolizumab group compared to placebo group, especially skin and general symptoms as well as pain (myalgia and arthralgia). Pharyngitis (13%), URTI (18%) and headache (37%) were very common side effects in healthy volunteers, who received mepolizumab. In study SB-240563/006, an increasing number of subjects with borderline QT prolongation were observed along time in all three treatment groups, including placebo (the IV

treatment was given at baseline, at week 4 and at week 8. The effect was somewhat dose-dependent.

- Severe adverse events: Significant proportion of subjects (37%) had serious adverse events during longer duration of treatment of HES patients, however, they were considered by the investigator to be related to the underlying disease. In study MHE100901, one subject had non-fatal SAEs that were considered to be possibly related to investigational treatment (optic neuritis, transverse myelitis, and spinal disorder). In the compassionate use program, one patient suffered from lobar pneumonia, one from polyarthritis and fever, one abnormal sputum and bronchitis and one hepatic vein thrombosis, which were considered mepolizumab-related.
- Deaths: 11 (7%) out of 156 subjects participating in HES clinical trials and compassionate use program have died as of the SAE by 30 April 2008. Two deaths (one due to angioimmunoblastic T-cell lymphoma and the other due to multi-organ failure/progression of HES) were considered possibly related to mepolizumab treatment (1.3% of all HES clinical trial patients) by the investigator. In the pivotal study, one death was reported (cardiac arrest), the subject received mepolizumab but the death was not considered drug-related. All deaths during longer treatments (Study MHE100901) were in previous mepolizumab group.
- Laboratory findings and exploratory markers: In HES-studies, low haemoglobin, low red blood cell count and low lymphocytes appeared more often in mepolizumab-treated patients than placebo-treated patients. Alkaline phosphatase showed mean increase in subjects in the mepolizumab group. Abnormal GGT and total bilirubin values were only observed in the mepolizumab groups group. High IL-5 levels could be detected in mepolizumab group in most of patients from the week 12 onward during the treatment period.
- Withdrawals because of adverse events: Five subjects were withdrawn in Study MHE100185 (4 placebo group, 1 mepolizumab group) five in Study MHE100901, and two in the Compassionate Use Program (overall 12 patients). None of the AEs leading to withdrawal in Study MHE100185 or the Compassionate Use Program were considered related to treatment by the investigator. In Study MHE100901, three of the five withdrawals were considered related to treatment by the investigator and included optic neuritis and transverse myelitis (reported as nonfatal SAEs), angioimmunoblastic T-cell lymphoma (fatal), and urticaria (potential infusion reaction was reported by the investigator on follow-up). In non-HES studies, adverse events leading to withdrawal have been related to exacerbation of the underlying disease; asthma (4 in multiple dose asthma studies; 1 in placebo and 3 in mepolizumab group); eosinophilic oesophagitis (1 in placebo group).
- Immunogenicity: In the pivotal study, five patients with positive samples of anti-mepolizumab antibodies have been detected (4 patients in mepolizumab group and 1 patient in placebo group). In EE patients, antibodies were detected in 2 patients with mepolizumab and in 1 patient with placebo. In single-dose studies, no mepolizumab-antibodies have been detected.

Missing safety data

- Limited data on safety of mepolizumab compared to placebo is available in the proposed target population; only 42 patients have been compared to placebo with proposed posology and indication (for 9 months).
- Short-term safety data is available from about 500 patients. However, long-term safety data with the proposed posology is missing. The extension study is ongoing with different posology and in the compassionate use program 13 patients have been given mepolizumab with variable dosing for 12 months or more.
- No sufficient amount of data have been provided on children or elderly patients with HES
- There is limited data presented on immunogenicity after repeated dosing of mepolizumab. In all studies 6 out of 329 tested subjects 4 were reported in the pivotal study with 43 patients (9%).
- There is not enough data to be able to evaluate rebound eosinophilia after mepolizumab treatment in HES

Other information

- The binding of mepolizumab to IL-5 has not been well characterised at the molecular level. There are uncertainties about potential binding of mepolizumab to the surface of leukocytes.

IV.4 Balance

HES is considered a rare disease under EU legislation (<5/10,000 people) and mepolizumab achieved Orphan Drug Designation in the EU in 2004. HES is a severe disease with high morbidity and mortality because of end organ damage and/or dysfunction, most often heart, skin, lungs, nervous system, liver and digestive tract. 100% of HES patients exhibit eosinophilia, 58% cardiovascular manifestations, 56% cutaneous, 54% neurologic, 49% pulmonary, 43% splenic, 30% hepatic, 23% ocular, and 23% gastrointestinal (GI) involvement and renal involvement. However, the level or duration of blood eosinophilia does not necessarily correlate with the degree of end-organ damage in HES. Instead, the severity of the clinical pathology does appear to reflect the extent of eosinophil activation in the tissues. The FIP1 negative forms of HES (lymphocytic and idiopathic, about 75% of all HES) respond to corticosteroid therapy. The corticosteroid sparing effect of mepolizumab would be of great benefit for these patients if they could reach disease control, relief of symptoms or longer survival. Unfortunately, this effect has not been demonstrated robustly, since no data on the reasons for patient withdrawals have been documented and presented. The level of eosinophils could be controlled in blood by mepolizumab, but at the tissue level, no control has been shown in HES patients.

The cumulative incidence of AEs was very high during the pivotal study in both mepolizumab (100%) and placebo groups (98%) during the pivotal study. Most AEs were considered as not related to study medication and the safety profile of mepolizumab can be considered good based on the presented data. Since the signs and symptoms of HES or the symptoms related to corticosteroids were not differentiated from AEs, it cannot be concluded if the HES symptoms or corticosteroid related adverse effects were diminished by mepolizumab treatment and the clinical relevance remains unclear. Also the effect on mortality has not been shown.

The applicant has not been able to present data on identical rational for withdrawals and identical following of the taper and rescue guidelines by the investigators in the pivotal study and show good control of HES symptoms during mepolizumab treatment (+/- small dose corticosteroid therapy). Therefore, the corticosteroid sparing effect cannot be considered established or the effects of mepolizumab of clinical benefit.

IV.5 Conclusions

The overall Benefit/Risk balance of Bosatria is negative.